Cce -H04212-14 (14) P024932 29.11.90

64 No 1 January 1989

ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

V. 64
1, 3-4
1989

rial 65

otations

vention after birth asphyxia *Whitelaw* 66

ticides in pediculosis capitis *Maunder* 69

nal articles

dostransferrin developmental deficiency ome *Kristiansson, Andersson, Tonnby, et al* 71

rsal of desferrioxamine induced auditory otoxicity during treatment with Ca-DTPA *ke, Hoffbrand, Aldouri, et al* 77

'happy puppet' syndrome of Angelman: w of the clinical features *), Pohl, Baraitser, et al* 83

e gastroenteritis in well nourished infants: parison of four feeding regimens *vay and Ireson* 87

uction of interferon in respiratory syncytial bronchiolitis *Isaacs* 92

vth and other factors affecting peak atory flow rate *Carson, Hoey, and Taylor* 96

ol holidays and admissions with asthma *and Lenney* 103

function eight years after atal ventilation *éasson, Lindroth, Mortensson, et al* 108

stress and job satisfaction at a children's ice *Woolley, Stein, Forrest, et al* 114

lly implantable venous access systems aediatric practice *x-Cater, Gilbert, Robinson, et al* 119

ptoms and signs of progressive ocephalus *Kirkpatrick, Engleman, and Minns* 124

Renal tubular proteinuria and microalbuminuria in diabetic patients *Gibb, Tomlinson, Dalton, et al* 129

Seronegativity and HIV infection *Lepage, Batungwanayo, and Van de Perre* 135

Short reports

Pyloric stenosis: congenital or acquired? *Rollins, Shields, Quinn, et al* 138

Plasma aldosterone and renin activity *Scammell and Diver* 139

Dysphagia due to oesophageal web *Puntis, Chapman, Proops, et al* 141

High compared with standard dose lipase pancreatic supplement *Robinson, Olinsky, Smith, et al* 143

Spontaneous regression of congenital epulis of the newborn *Jenkins and Hill* 145

Controversy

Shared care

Shared care in paediatrics *Bacon* 148

Families with congenital heart disease *Emery* 150

Joint work in paediatrics: a child psychiatry perspective *Sturge* 155

Personal practice

The investigation of haematuria *White* 159

Regular review

Hearts with one ventricle: current concepts and management *Sullivan and Taylor* 166

Current topic

Is the prevalence of asthma changing? *Anderson* 172

Correspondence 176

British Paediatric Association

Children in specialist hospital departments *Jackson* 181

Instructions to authors 183

BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

ISSN 0003-9888 ASTM CODEN: ADCHAK 64(1), 65-184, (1989)

Archives of Disease in Childhood

Editorial Committee

Editors: Bernard Valman and Malcolm Chiswick
Associate Editors: David Milner, Richard Robinson, Michael Silverman, and Brian Wharton

D P Addy
A G M Campbell
M J Dillon
I M Hann
M J R Healy
I A Hughes
D I Johnston

J W Keeling
J V Leonard
J K Lloyd
S P Lock
N McIntosh
P J Milla
E R Moxon

P O D Pharoah
L Polnay
N Richman
L Spitz
M J Tarlow
J F N Taylor
R M Winter

Technical Editor: Sue Heels
Editorial Assistant: Jacinta Marshall

Notes to Contributors
Papers for publication should be sent to the Editors, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR and should be prepared in accordance with the 'Instructions to authors' published in the January and June issues of the journal. Copies of these instructions may be obtained from the editorial office on receipt of a stamped addressed envelope.

Notice to Advertisers
Applications for advertising space and rates should be made to the Advertisement Manager, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR.

Notice to Subscribers
Archives of Disease in Childhood is published monthly. The annual subscription rates are £98 inland and £115 overseas (USA $165). Orders should be sent to the Subscription Manager, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. (For the convenience of readers in the USA subscription orders, with or without payment, may also be sent to *British Medical Journal*, Box 560B, Kennebunkport, Maine 04046. All enquiries however must be addressed to the Publisher in London.)

Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card.

All enquiries regarding air mail rates and single copies already published should be addressed to the publisher in London.

COPYRIGHT © 1989 by *Archives of Disease in Childhood*. This publication is copyright under the Berne Convention and the International Copyright Convention. All rights reserved. Apart from any relaxations permitted under national copyright laws, no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means without the prior permission of the copyright owners. Permission is not required to copy abstracts of papers or of articles on condition that a full reference to the source is shown. Multiple copying of the contents without permission is always illegal.

Second class postage paid, Rahway NJ. Postmaster: send address changes to: Archives of Disease in Childhood, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

Archives of Disease in Childhood, 1989, **64,** 65

Editorial

Style matters

We have copied this title from a well known weekly journal. Does it mean that this piece is about style or that style is important or both? We all know about the style of a dress or suit, but what is the ideal style for a paper and why do technical editors change words to conform with 'house style'? Swift said 'Proper words in proper places, makes the true definitions of a style'.[1]

Papers in scientific journals need to be written in a style in which the meaning is clear to all readers including those whose mother tongue is not English. The house style of a journal ensures uniformity and avoids unnecessary changes. Technical editors improve the clarity of original papers by removing ambiguous and imprecise words but they may alter the nuances of meaning and obscure the sparkle which readers find attractive in personal styles. Asher was highly critical of the dull *British Medical Journal* of his day and would have been pleased with his influence on the journal of today.[2] In the past, all papers were written in the passive but the occasional use of the personal pronoun may encourage a reader to start a paper on a boring subject.

After this month we shall publish results in Système Internationale (SI) units only and there will be no conversion factors to the old units. Papers will be less cluttered with numbers and easier to read. Other measures will improve clarity. A large proportion of our papers are now assessed by a statistical referee as well as a paediatric referee but detailed statistics, including p values, will be avoided in the summary which may otherwise become difficult to read.

The technical editor needs space to introduce instructions to the printer. This is not possible if the paper has single spacing and pages are not numbered. Papers which are typed so that all the words on the right hand edge are aligned (justified on the right) are neat but words are broken and this introduces ambiguities for the printer. Authors who ignore advice (page 183) will have their manuscripts returned to them before assessment.

References

[1] Swift J. A letter to a young gentleman. In: Hayward J, ed. *Swift—Gulliver's travels and selected writings in prose and verse.* London: Nonesuch Press, 1946:401. (Originally printed in London for J Roberts, 1721.)

[2] Asher R. Why are medical journals so dull? *Br Med J* 1958;**ii:** 502–3.

P24932

Archives of Disease in Childhood, 1989, **64**, 66–68

Annotations

Intervention after birth asphyxia

Despite improvements in fetal monitoring and neonatal resuscitation, every district general hospital has a number of full term infants every year who suffer from the effects of severe lack of oxygen before or during delivery. Approximately six per 1000 full term infants develop hypoxic-ischaemic encephalopathy and one per 1000 will die or survive with severe neurological disability.[1] In Great Britain, 300–400 children per year survive birth asphyxia with serious brain damage.

Paediatricians have vigorously tried to improve standards of neonatal resuscitation in the delivery ward but have found hypoxic-ischaemic encephalopathy a difficult problem to treat. A common attitude is that the damage has been done before arrival in the neonatal intensive care unit and treatment is too late to repair neural cell death. The prognosis has seemed so hopeless in some cases that withdrawal of intensive care has seemed the kindest solution.[2] Are we being too negative about the encephalopathy? This annotation discusses the emerging evidence that management after initial resuscitation may influence neurological outcome.

Hypoxic-ischaemic encephalopathy

After resuscitation a proportion of infants become neurologically abnormal during the next 48 hours. This encephalopathy can be clinically classified into: mild (irritability, poor sucking, and hypotonia), moderate (convulsions, lethargy, and appreciably abnormal tone), and severe (comatose with prolonged seizures and respiratory failure).[3] Out of 24 infants with moderate encephalopathy, one died and five survived with severe handicap. Out of 21 with severe encephalopathy, 13 died and three survived with severe handicap. Of the infants with mild encephalopathy, only one became handicapped and this child had a congenital myopathy.[1]

Convulsions

Generalised tonic-clonic convulsions should be treated as they tend to interfere with respiration and raise intracranial pressure. We start treatment with phenobarbitone 20 mg/kg intravenously as a loading dose.[4] If convulsions continue, paraldehyde 3 ml/kg/hour of a 5% solution is given intravenously until the seizures stop.[5] Continued seizures are treated with phenytoin 20 mg/kg and diazepam 0·3 mg/kg intravenously.

Postasphyxial seizures can be very resistant to treatment and intravenous clonazepam, lignocaine, chlormethiazole, and sodium valproate can be considered in such cases. Whether one should treat a comatose, ventilated baby who is having subtle seizures or purely electrical seizures is arguable. Neonatal seizures deplete the brain of high energy substrates and interfere with brain cell division[6] but large doses of anticonvulsants may have adverse effects: particularly respiratory and circulatory depression. It used to be thought that high dose barbiturate might have a protective effect after hypoxia by reducing cerebral metabolic requirements. A trial of thiopentone in severely asphyxiated infants, however, gave no evidence of benefit. Indeed hypotension was a troublesome side effect of thiopentone.[7]

Control of raised intracranial pressure

The brain commonly reacts to severe hypoxia by developing oedema over a period of 24–48 hours. The skull is able to accommodate some degree of brain swelling by squeezing cerebrospinal fluid out of the cranium. Moreover, neonates can tolerate some further brain swelling without the pressure rising because of the unfused sutures and the open fontanelles. Severe cerebral oedema can exceed the cranial compliance, however, and cause the pressure to rise above the normal upper limit of 6 mm Hg (0·80 kPa).[8] We have used the same subarachnoid pressure catheter technique as Levene *et al*[9] to monitor intracranial pressure in asphyxiated neonates and have confirmed their findings that raised pressure in some infants can be temporarily lowered by intravenous mannitol, that sustained intracranial hypertension (>15 mm Hg (2·00 kPa)) resistant to treatment has a very bad prognosis, and that some infants can have severe encephalopathy and bad outcome without raising intracranial pressure above 10 mm Hg (1·33 kPa).[9]

We have extensively investigated non-invasive measurement of intracranial pressure via the fontanelle and have found it too inaccurate for clinical decision making.[10] Although we have had no complications from subarachnoid catheterisation in 25 cases, the technique is highly invasive and has the potential to cause meningitis. No study has yet shown that invasive intracranial pressure monitoring and mannitol treatment improves later outcome.

Dexamethasone has been used for certain types of cerebral oedema associated with tumour or abscess. There is no evidence, however, that it gives benefit after birth asphyxia.[11]

Hyperventilation to produce hypocapnoea has been used to reduce raised intracranial pressure in adults. However, this effect is achieved by reducing cerebral blood flow which seems undesirable.

Circulatory support

Neonates are generally not good at raising arterial pressure in response to raised intracranial pressure (Cushing response) and the combination of low arterial pressure and raised intracranial pressure is particularly devastating. We have not found any normal survivors from a cerebral perfusion pressure (mean arterial pressure−intracranial pressure) below 20 mm Hg (2·67 kPa).

Hypovolaemia may be associated with asphyxia because of shunting of blood from the vasoconstricted fetus to the placenta, from blood loss, or from hypoxic capillaries leaking plasma into the interstitial space. Peripheral vasoconstriction, mean arterial pressure below 40 mm Hg (5·33 kPa), and metabolic acidosis are suggestive of hypovolaemia. Colloid at 10 to 20 ml/kg should be given intravenously and larger volumes may be necessary. Myocardial ischaemia may also occur with reduced cardiac output. This diagnosis would be suggested by finding cardiomegaly on chest radiography and ischaemic ST changes on electrocardiography. If arterial pressure remains low despite volume replacement, a dopamine infusion should be started after any remaining metabolic acidosis has been corrected with sodium bicarbonate. The dopamine infusion can start at 5 µg/kg/minute but should be increased to 10, 15, or 20 µg/kg/minute if mean arterial pressure does not reach 40 mm Hg (5·33 kPa).[12]

Cerebral protection

Studies of hypoxia in experimental animals have indicated that processes continuing for some hours after a hypoxic insult has ceased can bring about further cerebral damage. These mechanisms include a prolonged fall in cerebral blood flow (the no reflow phenomenon),[13] calcium loading of mitochondria activating phospholipase,[14] release of oxygen free radicals,[15] and excitatory amino acids such as glutamate.[16] Steen *et al* showed that the calcium channel blocker nimodipine improved survival when given after complete cerebral ischaemia in primates.[17] Thiringer *et al* carried out a randomised trial of oxygen free radical scavengers (methionine, mannitol, and magnesium sulphate) and the calcium channel blocker lidoflazine in lambs subjected to acute umbilical cord occlusion.[18] She found that the lambs treated within 5 minutes of resuscitation retained cerebral blood flow better than controls. The treated lambs also had better somatosensory evoked potentials and cerebral cortical function. There are no published studies on glutamate antagonists, free radical scavengers, or calcium channel blockers in human neonates.

Prognosis

Nelson and Ellenberg found that an Apgar score of <4 at 20 minutes gave a 57% chance of cerebral palsy in survivors.[19] Steiner and Nelligan found that all full term infants who failed to establish respiration by 30 minutes subsequently had spastic quadriplegia and mental retardation.[20] It has been a common practice to discontinue further resuscitation if there is no respiratory effort after 30 minutes. Infants with severe encephalopathy who have persistently raised intracranial pressure (>15 mm Hg (2·00 kPa)) resistant to mannitol also have an extremely poor outlook. In the future, electroencephalography, cerebral blood velocity by Doppler, and phosphorus magnetic resonance spectroscopy may help to give us an accurate prognosis at an early stage. Asphyxiated infants who are assessed very early to have a bad prognosis are the ones who should be considered for therapeutic trials of cerebral protection.

References

1 Levene MI, Sands C, Grindulis H, Moore JR. Comparison of two methods of predicting outcome in perinatal asphyxia. *Lancet* 1986;**i**:67–8.

2 Whitelaw A. Death as an option in neonatal intensive care. *Lancet* 1986;**ii**:328–31.

3 Levene MI, Kornberg J, Williams THC. The incidence and severity of post-asphyxial encephalopathy in full term infants. *Early Hum Dev* 1985;**11**:21–6.

4 Painter MJ, Pippenger C, Macdonald H, Pitlick P. Phenobarbital and diphenylhydantoin levels in neonates with seizures. *J Pediatr* 1978;**92**:315–9.

5 Giacoia GP, Gessner PK, Zaleska MM, Boutwell WC. Pharmacokinetics of paraldehyde disposition in the neonate. *J Pediatr* 1984;**104**:291–5.

6 Wasterlain C, Plum F. Vulnerability of developing rat brain to electroconvulsive seizures. *Arch Neurol* 1973;**29**:38–45.

7 Eyre JA, Wilkinson AR. Thiopentone induced coma after severe birth asphyxia. *Arch Dis Child* 1986;**61**:1084–9.

[8] Kaiser A, Whitelaw A. Normal cerebrospinal fluid pressure in the newborn. *Neuropediatrics* 1986;**17**:100–2.

[9] Levene MI, Evans DH, Forde A, Archer LNJ. Value of intracranial pressure monitoring of asphyxiated newborn infants. *Dev Med Child Neurol* 1987;**29**:311–9.

[10] Kaiser A, Whitelaw AGL. Non-invasive monitoring of intracranial pressure—fact or fancy? *Dev Med Child Neurol* 1987;**29**: 320–6.

[11] Levene MI, Evans DH. The medical management of raised intracranial pressure following severe birth asphyxia. *Arch Dis Child* 1985;**60**:12–6.

[12] Ferez CA, Reimer JM, Schreiber MD, Warburton D, Gregory GA. Effect of high dose dopamine on urine output in newborn infants. *Crit Care Med* 1986;**14**:1045–9.

[13] Ames A, Wright RL, Kowada M. Cerebral insult II. The no reflow phenomenon. *Am J Pathol* 1968;**52**:437–53.

[14] White B, Wiegenstein JG, Winegar CD. Brain ischemic anoxia. Mechanisms of injury. *JAMA* 1984;**251**:1586–90.

[15] McCord JM. Oxygen-derived free radicals in post-ischemic tissue injury. *N Engl J Med* 1985;**312**:159–63.

[16] Meldrum B, Evans M, Griffiths T, Simon R. Ischemic brain damage: the role of excitatory activity and of calcium entry. *Br J Anaesth* 1985;**57**:44–6.

[17] Steen PA, Gisvold SE, Milde JH, *et al.* Nimodipine improves outcome when given after complete cerebral ischemia in primates. *Anesthesiology* 1985;**62**:406–14.

[18] Thiringer K, Hrbek A, Karlsson, Rosen KG, Kjellmer I. Postasphyxial cerebral survival in newborn sheep after treatment with oxygen free radical scavengers and a calcium antagonist. *Pediatr Res* 1987;**22**:62–6.

[19] Nelson KB, Ellenberg JH. Apgar scores as predictors of chronic neurologic disability. *Pediatrics* 1981;**68**:225–32.

[20] Steiner H, Nelligan G. Perinatal cardiac arrest. Quality of the survivors. *Arch Dis Child* 1975;**50**:696–702.

A WHITELAW
Department of Paediatrics and
Neonatal Medicine,
Hammersmith Hospital,
DuCane Road,
London W12 0HS

Archives of Disease in Childhood, 1989, **64,** 69–70

Insecticides in pediculosis capitis

Ectoparasitosis treatment provides a rare example of the deliberate use of insecticides on human beings. As the bulk of medical insecticide is employed against head lice, scabies lying second, most patients are children. Those prescribing insecticides may wish to understand some of the principles involved.

Insecticide penetration

Insecticides enter insects and ova in accordance with passive physical laws, without active metabolic intervention.[1] The outermost layer of insect cuticles is lipoid and uptake from pediculicidal formulations is controlled by the partition laws.

Insecticide moves from higher concentrations, proportional to saturation, into cuticle waxes, where there is greater saturation deficit. The dose then moving on through the integument per unit area is described by the laws of diffusion, $D=(c_1-c_2)\ t\ k$ where c_1 and c_2 are the insecticide concentrations at the outer and inner boundaries of the integument and c_1-c_2 the concentration gradient driving the diffusion. The dose is equally determined by t, the time of exposure. Twice the exposure doubles the dose. The constant k describes the particular cuticle involved.[2]

Louse cuticles, having the lowest known lipid content of any insect group,[3] are comparatively effective barriers to insecticides, which are always highly lipophilic. Unless k is modified by suitable formulation, then either higher concentrations of insecticides or longer exposure times must be employed against lice than against other insects, and these will equally be experienced by patients.

Concentration and time are all important as regards the lice, the actual quantity of insecticide present being irrelevant. As regards human toxicity, however, it is the total quantity present which is vitally important. If there isn't enough insecticide there, then the patient cannot be harmed. The aim of pediculicide formulation is to maximise the dose acquired by the insects while minimising the amount of insecticide employed.

Formulation types

Formulators achieve these objectives in various ways.

(1) PHASE SEPARATION LOTIONS

Small quantities of insecticide are dissolved in small volumes of lipid, typically forming solutions of about 20%. Adjuvants may be added to reduce the solubility and so raise the percentage saturation, ideally to just below complete saturation. This solution is then emulsified into a larger volume of water, to which stabilisers and perfumes may be added. The resulting water based emulsion may have an overall concentration of no more than 0·5%. On the head it separates into its constituent phases. The lice and eggs become coated with a *thin* lipid film containing 20% insecticide, but at perhaps 70% saturation, while the aqueous phase merely wets the hair.

A typical two hour application may subject lice to 8000 arbitrary units of dose, although no more than 100 mg of insecticide may be present on the head.[4]

(2) EVAPORATING LOTIONS

A small quantity of insecticide is dissolved in a large volume of isopropanol, to which up to 40% of water has been added to lower the solubility and so raise percentage saturation. When on the head, spirit and water evaporate together, being an approximate constant boiling mixture. The insecticide concentrates to a fine film coating lice, eggs, and hair. High effective concentrations are achieved using low quantities of insecticide and initial overall concentrations of no more than 0·5%.

(3) INSECTICIDAL CONDITIONING SHAMPOO

Shampoos are immediately diluted with much water. This is not necessarily bad because if the insecticide is very soluble in the organic materials present the water greatly raises the percentage saturation in the final mixture. Many an insecticidal shampoo only kills lice when diluted.

When insecticides were first incorporated into detergent shampoos the formulations had only about three minutes in which to act and were poorly effective. Even a 1% shampoo at 80% of saturation can only amount to 240 arbitrary units of dose over three minutes.

Modern good quality shampoos now not only remove dirty oils, but replace them with conditioning lipids. If these now contain the insecticides a substantive effect is possible, enhancing pediculicidal activity, but still the short contact time is a problem which needs circumvention.

Limits to insecticide efficacy

In large populations of insects tolerances to insecticides are normally distributed about a mean, so that dose/response plots produce sigmoid curves, the upper ends of which are effectively asymptotic, approaching but never meeting the 100% mortality level. There is in theory no dose which just kills all of an infinitely large population.

In practice, even doses which give 99% mortality must be multiplied many times to give 99·9%. Manufacturers' claims for 100% mortalities must be viewed with suspicion.

Insecticides act on nervous systems, which young insect eggs do not yet possess. Mature eggs have a fully formed louse, with its own cuticle, still within the intact eggshell. Consequently both new laid and mature eggs are exceedingly difficult to kill, especially with short contact times. Ovicidal action is invariably unsatisfactory with single applications of insecticidal shampoo. In practice this need not matter, nor does it usually help to raise the ovicidal effect of the shampoo, for this is virtually impossible adequately to do, and quite unnecessary providing rational treatment strategies are used to turn the insects' own biology against themselves.

Treatment regimes for shampoo

In nature head louse eggs hatch in six to eight days and the nymphs require a further 10 to 12 days before they can themselves lay fresh eggs.[5]

Clearly, then, shampoos should be used as a course of treatment, preferably using monitored unit applications, say twice a week for two weeks. The first application should kill all walking stages but only some eggs. The second kills any newly hatched nymphs and a further proportion of eggs. By the third application all eggs must be hatched or dead, any surviving nymphs are killed and there are no adults left to lay new eggs. A fourth application allows for human error.

When used as a course of treatment, any insecticidal shampoo with adequate action against nymphs and adults will be fully effective. Naturally, medical entomologists have always preferred lotions, where a total cure can often be achieved in one step, but the general public will need much education before modifying their preference for shampoo.

Insecticidal shampoos, however, should still be regarded as medicines and prescribed for a defined course of treatment with a firm termination: the indefinite use of powerful insecticides is highly undesirable.

References

[1] Matsumura F. *Toxicology of insecticides*. 2nd ed. New York: Plenum Press, 1985.

[2] Busvine JR. *A critical review of the techniques for testing insecticides*. London: Commonwealth Institute of Entomology, 1957.

[3] Lovell GA. Studies on the cuticle of the human body louse, *Pediculus humanus humanus*. London: University of London, 1982. (PhD thesis.)

[4] Maunder JW. Human lice: biology and control. *Royal Society of Health Journal* 1977;97:29–32.

[5] Maunder JW. The appreciation of lice. *Proceedings of the Royal Institution* 1983;55:1–31.

J W MAUNDER

Medical Entomology Centre at the
University of Cambridge,
Department of Applied Biology,
Pembroke Street, Cambridge CB2 3DX

Archives of Disease in Childhood, 1989, **64,** 71–76

Original articles

Disialotransferrin developmental deficiency syndrome

B KRISTIANSSON,* M ANDERSSON,† B TONNBY,‡ AND B HAGBERG*

**Department of Pediatrics, Östra Hospital, Gothenburg University, Göteborg, †Department of Neurology, Sahlgrenska Hospital, Gothenburg University, Göteborg, and ‡Department of Pediatrics, Central Hospital, Halmstad, Sweden*

SUMMARY Seven mentally deficient children and adolescents (three pairs of siblings and one singleton) were studied. A peculiar external appearance, a characteristic neurohepatosubcutaneous tissue impairment syndrome and, as a biological marker, an abnormal sialic acid transferrin pattern were characteristic features. All seven seemed odd from birth and prone to acute cerebral dysfunction during catabolic states. Abnormal lower neurone, cerebellar, and retinal functions dominated from later childhood. The disialotransferrin pattern found in serum and cerebrospinal fluid is thought to be the biological marker of a newly discovered inborn error of glycoprotein metabolism with autosomal recessive inheritance.

Children who have unexplained developmental deficiency and similar, peculiar appearance and behaviour are diagnostic challenges. The ultimate aim is to establish diagnoses from the cause of the deficiency. When this is not feasible, eponyms, acronyms, or descriptive names may help in setting diagnoses, which is important for genetic counselling and prognosis and information, and sometimes for treatment.

A common biochemical marker may help in establishing a diagnosis and in tracing the basic defect, and may be useful for prenatal diagnosis. We recently succeeded in finding such a marker for three pairs of siblings and one single child in four unrelated families. The marker, an abnormal sialic acid transferrin pattern detectable in both serum and cerebrospinal fluid was found by Jaeken *et al* in twin sisters with psychomotor retardation, delayed nerve conduction velocity, increased protein in the cerebrospinal fluid, and numerous abnormalities in the serum.[1 2] Quite recently Jaeken *et al*[3] found additional information and reported two more cases. It now seems most likely that their four patients and our seven represent the same—or a closely allied—condition about which we have collected a considerable amount of clinical and laboratory data over the years while searching for the diagnosis and origin.

The obvious common clinical manifestations are so characteristic that two of our families, unaware of each others' existence, immediately recognised the almost identical appearance and motor behaviour of their children when they met by chance in the street on holiday in a small Swedish town.

The aim of this paper is to present the disialotransferrin developmental deficiency syndrome, its clinical characteristics, and its common biochemical marker and to summarise the main diagnostic investigations carried out that so far have not discovered the aetiology.

Methods

Isoelectric focusing of serum and cerebrospinal fluid was carried out in flat beds of polyacrylamide gel and silver staining according to previously described methods.[4] The transferrin content of each sample was determined by electroimmunodiffusion. About 0·8 μg of transferrin was applied to the isoelectric focusing gel.[5] Crossed immunoelectrophoresis was carried out in a 1% agarose gel. The gel was prepared in 0·07 M trometamol (TRIS)/0·02 M barbitone buffer, pH 8·2, containing 3·4 mM calcium lactate and 1% sodium azide. The gel was cast on a Gelbond (FMC corporation) polyester film. Twenty microlitres of rabbit antihuman transferrin antibodies (Dakopatts) were added to 30 ml of agarose. After the first dimension electrophoresis, the part of the isoelectric focusing gel containing transferrin was transferred on a piece of Gelbond to an antibody free zone on the agarose gel. Electrophoresis in the second dimension was run at 15–20 V/cm for six hours.

Patients

Seven children were studied (table). Once the two index cases (cases 1 and 2) were found to carry the characteristic changes of the transferrin, five other children (cases 3–7) were investigated because of clinical, developmental, and behavioural similarities. The series comprised three boys and four girls, three pairs of siblings and one singleton in four unrelated families. No consanguinity was traced, and no child with a similar disease had been born before according to grandparents, uncles, aunts, or cousins. All seven children have been followed up by us from infancy. One couple of parents had samples of their serum and cerebrospinal fluid investigated.

For comparison serum samples from seven children with abnormal liver function were investigated to find out whether the transferrin changes reflected impaired liver function.

Eight thousand routine isoelectric focusing examinations of cerebrospinal fluid and serum carried out at the Sahlgrenska Hospital cerebrospinal fluid laboratory during the years 1983–1987 were retrospectively reviewed for similar aberrations in the transferrin pattern.

Results

THE MARKER

All seven children had a predominating band of transferrin containing two molecules of sialic acid (disialotransferrin) in both cerebrospinal fluid and serum, sometimes stronger than the band of tetrasialotransferrin, which is usually the predominant band (fig 1).

In the two parents of one pair of siblings the transferrin patterns in serum and cerebrospinal fluid pattern were normal. In the seven children with abnormal liver function, the transferrin patterns in serum were normal. The described transferrin pattern was not detected in the 8000 samples of cerebrospinal fluid and serum except for two patients who had been investigated for neurological symptoms caused by severe alcohol abuse.

Table *Age, sex, perinatal data, and clinical characteristics*

Family	*A*		*B*	*C*		*D*	
Case No	*1*	*2*	*3*	*4*	*5*	*6*	*7*
Sex	*Boy*	*Girl*	*Boy*	*Girl*	*Boy*	*Girl*	*Girl*
Age (years)	*3*	*5*	*11*	*13*	*16*	*18*	*21*
Birth weight (g)	*3600*	*3500*	*2200*	*2800*	*3500*	*3200*	*2900*
Gestational age (weeks)	*40*	*40*	*36*	*41*	*40*	*40*	*38*
Clinical picture							
General characteristics:							
Early floppiness	+	+	+	+	+	+	+
Gluteal fat pads	−	+	+	+	−	+	+
Failure to thrive	+	+	+	+	+	+	+
Inverted nipples	+	+	−	+	−	+	+
Joint restrictions	−	−	+	+	+	+	+
Facial characteristics:							
High bridge of the nose	+	+	+	+	+	+	+
Prominent jaw	−	+	+	+	+	+	+
Large external ears	+	+	+	+	+	+	+
Ocular abnormalities:							
Squint	+	+	+	+	+	+	+
Retinitis pigmentosa	−	−	−	+	+	+	+
Dystrophic maculas	+	+	+	+	+	−	−
Neurological characteristics:							
Lower neurone weakness	+	+	+	+	+	+	+
Mental retardation	+	+	+	+	+	+	+
Microcephaly	−	+	+	+	+	−	−
Epilepsy	−	+	+	+	−	+	+
Stroke like episodes	−	+	+	+	−	+	+
Neurogenic hearing impairment	−	−	−	−	+	+	+
Skeletal abnormalities:							
Osteopenia	−	−	+	−	+	+	+
Kyphoscoliosis	−	−	+	+	+	+	+
Delayed skeletal maturation	+	−	+	+	−	+	+

+=Present.
−=Absent.

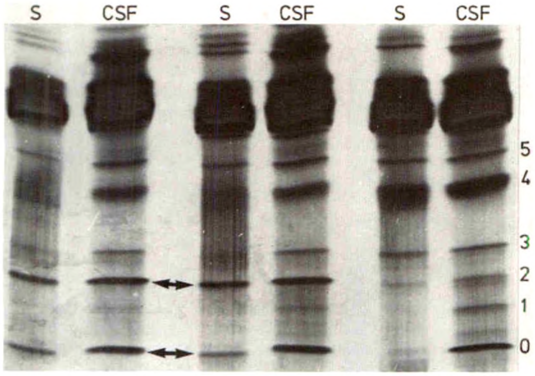


Fig 1 *Isoelectric focusing of samples of serum (S) and cerebrospinal fluid (CSF) from two affected children (left and middle) and one healthy control (right). Numbers to the right indicate bands corresponding to transferrin with 0–5 molecules of sialic acid. Arrows indicate the characteristic marker.*

SIGNS AND SYMPTOMS (table)

During the neonatal period unspecific features of ill health like respiratory distress syndrome, polycythaemia, hyperbilirubinaemia, and suspected septicaemia were noticed in five of the children, and only two (cases 1 and 2) had entirely uneventful neonatal periods. All seven affected children were extremely floppy infants from birth or from the early postnatal period. Feeding difficulties and diarrhoea were obvious problems from around 6 months of age, at which time signs of liver disease were noticed. The gastrointestinal symptoms were accompanied by a slowing of growth at the age of 6–8 months and a subsequent 'catch-up' in growth between 12 and 18 months of age when the intestinal symptoms subsided. Mild non-progressive liver disease persisted during the first years, with slightly increased liver transferase activities, mild hepatomegaly, and morphological changes.

During early infancy, remarkable fat pads (which later disappeared) were noticed over the buttocks in five of the seven children (fig 2). Particularly on the lower parts of the body, the skin tended to be thick and adherent (peau d'orange), or like patchy sclerema. The following additional characteristics were recorded: a dysmorphic facial appearance (figs 2 b and d) with a high bridge to the nose and eyes close together; an asymmetric, small, or even microcephalic skull; a convergent squint and large external ears; a prominent jaw with a short neck; and inverted nipples and restricted lower limb joints contrasting with an otherwise extreme floppiness.

Early psychomotor development was delayed in all children, particularly from the age of 4–5 months, when gross motor abilities lagged behind. The developmental retardation was subsequently found to be generalised, affecting principally gross motor development but also fine motor, social, and mental performances. The children's ability to sit, crawl, stand up, and walk with support was severely delayed. They learnt to move by rolling over or crawl-shuffling, and (when older) wheel chairing. Hand skill development seemed to be less affected than gross motor performance. Some of them learned to make simple drawings but not to read or write. They managed to eat by themselves and to use a knife and fork, and they could be toilet trained. Their intellectual capacity progressed through the first decade of life. Their mental ability permits them to understand spoken words but their own active speech is limited. The children have developed a simplified language comprehensible to siblings and parents and useful for family social life.

The neurological manifestations successively developed towards those of a severe weakness of a lower neurone type affecting both legs with additional traits of cerebellar ataxia and coordination difficulties. Tendon reflexes became increasingly weak and were impossible to elicit after 1 year of age. All the children have ocular abnormalities; severe alternating squint ($n=7$), retinal pigmentation ($n=4$), and dystrophic maculas ($n=3$).

Five have presented with 'stroke like episodes' during or after acute infections. Three children have had recurrent transient hemiparesis. One girl developed a Reye like syndrome after varicella (no liver biopsy was carried out). Another girl has twice (during a common cold on each occasion) become comatose for one to four days without any obvious cause; intracranial pressure, glucose homoeostasis, acid base balance, liver function (including the urea cycle), and mitochondrial and peroxisomal function have all been normal during these periods. After the first incident the girl was blind for three months; her vision then reappeared. One child (case 2) had recurrent severe pericardial effusions during infancy and pericardectomy was carried out because of cardiac tamponade.

The two eldest sisters (family D) still have no signs of pubertal maturation, and extensive investigations show that they have primary hypogonadism. In contrast, case 5 has matured normally and passed puberty and his sister is at pubertal stage 2 at the age of 12 years.

LABORATORY INVESTIGATIONS

As well as studies on the marker, extensive additional investigations have been carried out over the years. Tests for intrauterine infections, metabolic disorders (amino acid abnormalities, organic aci-

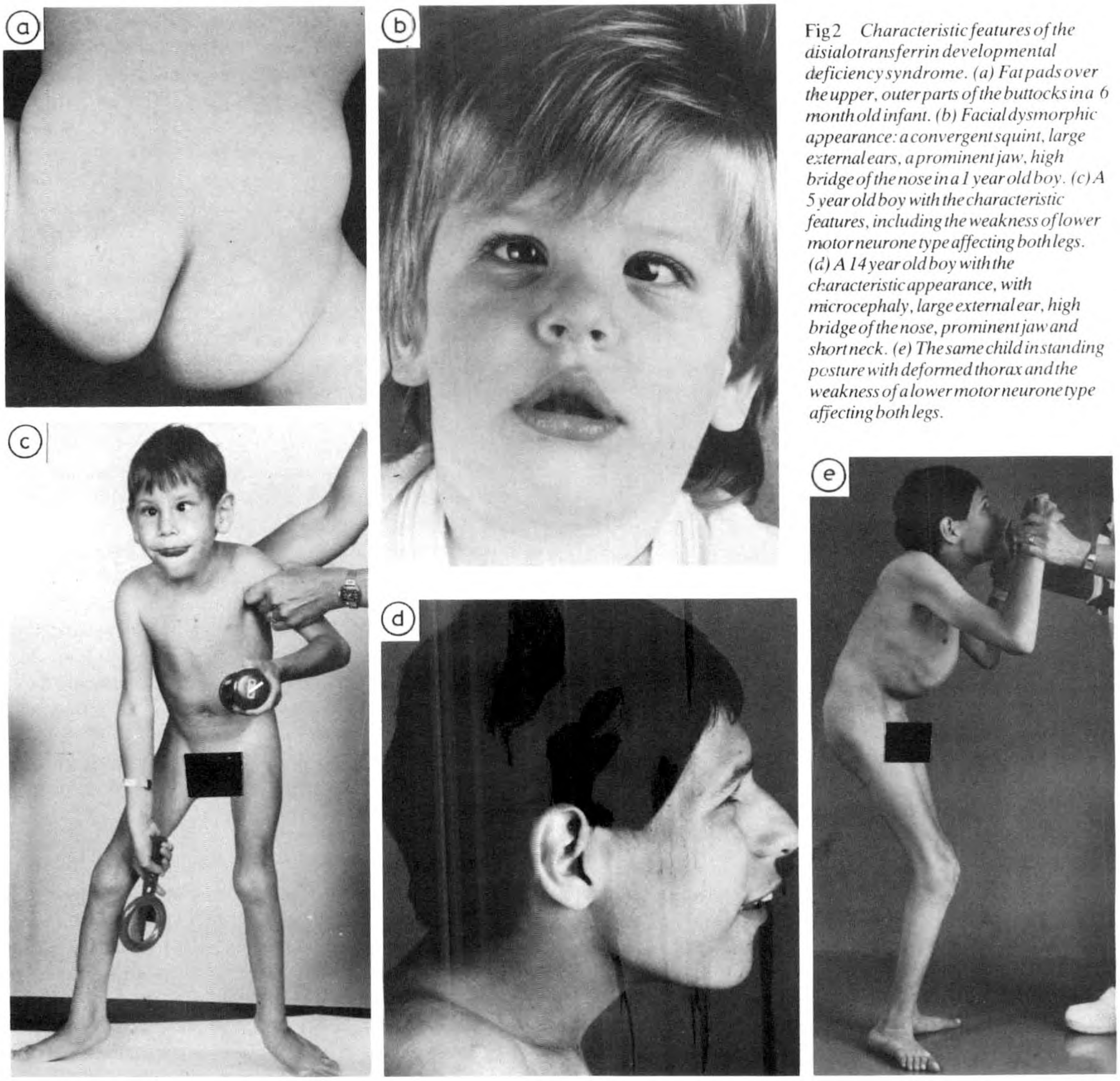


Fig 2 *Characteristic features of the disialotransferrin developmental deficiency syndrome. (a) Fat pads over the upper, outer parts of the buttocks in a 6 month old infant. (b) Facial dysmorphic appearance: a convergent squint, large external ears, a prominent jaw, high bridge of the nose in a 1 year old boy. (c) A 5 year old boy with the characteristic features, including the weakness of lower motor neurone type affecting both legs. (d) A 14 year old boy with the characteristic appearance, with microcephaly, large external ear, high bridge of the nose, prominent jaw and short neck. (e) The same child in standing posture with deformed thorax and the weakness of a lower motor neurone type affecting both legs.*

daemias, organic acidurias, glycogenoses, and mitochondrial and peroxisomal disorders), and malabsorptive disorders of the pancreas and intestines have all been unhelpful. All seven children have excreted an excess of oligosaccharides and sialic acid in their urine, although highly variable in amounts and with no consistent change of the oligosaccharide pattern. Excess amounts of mucopolysaccharides were found in three of the children, always with an increase of chondroitin sulphate. Nevertheless, primary defects in mucopolysaccharide, oligosaccharide, and glycogen metabolism could be ruled out, as could the diseases of glucoprotein degradation like aspartylglucosaminuria and sialidosis.

In two of the children (case 6 and 7) low concentrations of pre β lipoproteins and β lipoproteins were found during infancy, but later both cholesterol and triglyceride concentrations were normal in serum, as in the other five children.

In one child (case 3) suspected of having familial mucolipidosis, several acid hydrolases (α-fucosidase, β-hexosaminidase, β-glucuronidase, iduronosulphate sulphatase) were clearly increased in serum. In four children α_1-antitrypsin activity was abnormal, probably reflecting an abnormal sialic acid pattern similar to that of transferrin.

Protein was increased in the cerebrospinal fluid during infancy (0·6–1 g/l) in all cases, with signs of damage to the blood brain barrier, which later reverted to normal.

Nerve conduction velocity was reduced in all children after the age of 6 to 8 months, distal parts being more affected than proximal ones. Electromyography was normal in all. Computed tomography showed cerebellar hypotrophy in three of the six children investigated. It was normal in two, and the sixth child had diffuse calcification in the white matter and a low density area in the parieto-occipital region.

Biopsy specimens of the sural nerve were obtained from five children: at 6 months of age that from one boy was normal on both light and electron microscopy. The other four specimens were taken between 1 and 10 years of age and showed mild forms of neuronal-axonal neuropathy. Biopsy specimens of muscle were obtained from all seven children; these were either normal or only slightly abnormal on histological examination, reflecting the neuropathy. Biopsy specimens of liver were taken from three of the children between the ages of 6–24 months. All displayed steatosis with fat vacuoles and fibrosis. In one child a cirrhotic pattern was discerned. Glycogen seemed to be increased. After the age of 2 years, however, the liver seemed to be less affected, and activities of liver transferases, α-fetoprotein, and γ-glutamyltranspeptidases returned nearly to normal. At the age of 12 and 14 years, two had liver biopsy specimens that were normal.

Discussion

In this study a biological marker—abnormal transferrin with a characteristic isoelectrophoretic pattern—was found in both serum and cerebrospinal fluid of seven mentally deficient children all of whom had a remarkable combination of peculiar clinical signs. These children had seemed clinically odd from birth or early infancy with anomalous appearance, floppiness, respiratory problems, liver dysfunction, unusual 'peau d'orange' skin, and fat pads on the buttocks, as well as deviating psychomotor development. Later in childhood they developed a neurological disorder with severe weakness of the lower neurone type affecting both legs, combined with cerebellar signs and atrophy, epilepsy, impaired vision with macular dystrophy and retinal pigmentation, neurogenic hearing defects in some, pronounced secondary kyphoscoliosis with a hump, peculiar fibrous restricted movements in the hip and knee joints, and unexplained osteopenia. There was a high risk of acute cerebral dysfunction during or after infectious diseases or other catabolic states. Episodes similar to Reye's syndrome with stupor or coma then tended to develop, but without hyperammonaemia, hypoglycaemia, or acute liver dysfunction.

To judge from our older patients, the long term course seems to be stationary as regards mental performance. Both gross and fine motor performance improved during the years of observation, but a slow, progressive downhill tendency was seen in both the lower neurone and the cerebellar functions. Differential diagnostic considerations were mainly lysomal disorders, but the combination of dysmorphic symptoms and slowly progressive neurological disabilities have suggested associations with the group of peroxisomal disorders. Laboratory tests, however, have so far excluded traditional groups of intermediary metabolic disturbance, as well as oligosaccharidoses, mucopolysaccharidoses, glycogenoses, mitochondrial, and peroxisomal diseases. The laboratory findings were all unspecific and of no diagnostic help except for the characteristic changes of the transferrin.

The actual abnormality in transferrin was described by Jaeken *et al*[1–3] and associated with a set of clinical signs that might well tally with those of our cases. The disialotransferrin band in some children is even stronger than the tetrasialotransferrin band, which is usually the predominating one. A similar sialic acid-transferrin pattern is however, also recognised in adult alcoholics during periods of abuse.[6 7] In our experience, the pattern caused by alcohol is often much less pronounced than in the children described here. It is known to be dose dependent, however, and among the 8000 samples that we re-examined there were two with patterns indistinguishable from that of the disialotransferrin developmental deficiency syndrome. The well known neuronal cell and tract impairments caused by alcohol are of certain interest in this connection.[8] The reason for the changes in the sialic acid transferrin pattern in alcoholics is unknown but there is some evidence that ethanol may inhibit glycosylation of glycoproteins with derangement of the carbohydrate composition of the glycoproteins, transferrin in particular.[9] It would not be unreasonable to suspect that the disialotransferrin-developmental deficiency syndrome described in this study might as regards clinical manifestations be the effect of similar mechanisms, perhaps representing an inborn error of metabolism.

References

[1] Jaeken J, van Eijk HG, van der Heul C, Corbeel L, Eeckels R,

Eggermont E. Sialic acid-deficient serum and cerebrospinal fluid transferrin in a newly recognized genetic syndrome. *Clin Chim Acta* 1984;**144:**245–7.

[2] Jaeken J, Vanderschureren-Todeweycky M, Caesar P, *et al.* Familial psychomotor retardation with markedly fluctuating serum prolactin, FSH and GH levels, partial TBG-deficiency, increased serum arylsulphatase A and increased CSF protein: a new syndrome? *Pediatr Res* 1980;**14:**179.

[3] Jaeken J, Eggermont E, Stibler H. An apparent homozygous X-linked disorder with carbohydrate-deficient serum glycoproteins. *Lancet* 1987;**i:**1398.

[4] Wikkelsö C, Andersson M, Andersson R, Blomstrand C. Isoelectric focusing followed by silver staining. *Eur Neurol* 1984;**23:**306–12.

[5] Laurell C-B, Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies. *Anal Biochem* 1966;**15:**45–52.

[6] Stibler H, Sydow O, Borg S. Quantitative estimation of abnormal micro-heterogeneity of serum transferrin in alcoholics. *Pharmacol Biochem Behav* 1980;**13:**47–51.

[7] Stibler H, Borg S. Carbohydrate composition of serum transferrin in alcoholic patients. *Alcoholism—Clinical and Experimental Research* 1986;**10:**61–4.

[8] Noronha AB, Druse MJ. Maternal ethanol consumption and synaptic membrane glycoproteins in offspring. *J Neurosci Res* 1982;**8:**83–97.

[9] Takase S, Takeda A, Tsutsumi M, Matsada Y. Biochemical markers of chronic alcoholism. *Alcohol* 1985;**2:**405–10.

Correspondence to Dr B Kristiansson, Department of Pediatrics, Östra Hospital, S-416 85 Gothenburg, Sweden.

Accepted 26 May 1988

Archives of Disease in Childhood, 1989, **64**, 77–82

Reversal of desferrioxamine induced auditory neurotoxicity during treatment with Ca-DTPA

B WONKE,* A V HOFFBRAND,† M ALDOURI,† D WICKENS,‡ D FLYNN,¶ M STEARNS,§ AND P WARNER§

*Departments of *Haematology and ‡Chemical Pathology, Whittington Hospital, and Departments of †Haematology, ¶Paediatrics and §Ear, Nose and Throat, Royal Free Hospital, London*

SUMMARY Auditory neurotoxicity occurred in 13 (26%) of 50 evaluable patients receiving long term desferrioxamine chelation. In five of these patients, all of whom were receiving high doses of desferrioxamine, the toxicity caused deafness. These five patients were treated with subcutaneous calcium diethylene triamine pentacetic acid (Ca-DTPA) with zinc supplements instead of desferrioxamine, and their hearing improved during periods of seven to 19 months. Their serum iron concentrations remained unchanged. We suggest that all patients receiving long term desferrioxamine should have audiometric assessments at 6–12 monthly intervals. Ca-DTPA with oral zinc supplements should be considered as alternative to desferrioxamine as an iron chelating treatment in patients with auditory neurotoxicity.

Iron overload is a well recognised complication of long term transfusion treatment. In 1963 desferrioxamine was first introduced and given both intramuscularly and intravenously. In 1976, however, the subcutaneous delivery of the drug by a portable infusion pump was introduced.[1 2] During the past 10 years long term parenteral treatment of desferrioxamine at doses of 20–50 mg/kg/day has been used to maintain iron balance in patients on regular transfusion regimens with stores about five to 10 times normal.[3]

Desferrioxamine is a comparatively non-toxic drug with few side effects. In recent years, however, high doses of desferrioxamine given either intravenously or subcutaneously were found to be toxic to the eyes and ears.[4–7] In the present study the incidence of auditory abnormalities was assessed in a group of 54 patients with thalassaemia major who were receiving regular blood transfusions and long term treatment with subcutaneous desferrioxamine. In five patients, desferrioxamine treatment was withdrawn because of high tone deafness, and iron chelation was continued with calcium diethylene triamine pentacetic acid (Ca-DTPA). The effects of stopping desferrioxamine on the hearing of these patients have been assessed as well as the efficacy of Ca-DTPA compared with desferrioxamine as a long term iron chelator.

Patients and methods

Fifty four patients aged 5–35 (mean 19) years with homozygous β thalassaemia were studied. There were 26 male and 28 female patients, and they had received from 53 to 608 (mean 326) units of blood. Forty nine patients were receiving 40–50 mg/kg body weight of desferrioxamine, and five patients 85–160 mg/kg body weight subcutaneously over 8–12 hours on five or six nights each week.

In addition, the patients were given desferrioxamine 1–2 g/unit of blood intravenously at the time of transfusion. Oral vitamin C 100–200 mg daily was added to this treatment. The duration of treatment with desferrioxamine ranged from two to nine years. Plasma zinc, copper, caeruloplasmin, magnesium, calcium, and 24 hour urinary iron and zinc concentrations were measured initially and then monthly in the five patients receiving treatment with Ca-DTPA.

All patients were tested audiometrically. Before testing, histories were taken to make sure the patients did not have middle ear disease or had had operations that might have affected inner ear function. All patients were asked about possible acoustic trauma, head injury, and the use of previously known ototoxic drugs (such as gentamicin); each patient was also examined and assessed. Four of the 54 patients were excluded because definite aetiological factors were identified—in particular, they reported that they had been exposed to continuous excessive amounts of sound or to ototoxic drugs. Pure tone audiometry was carried out in a sound proofed booth; masking was used when indicated and the equipment was calibrated to national standards. Bone conduction was tested when a hearing loss had been identified to indicate whether the loss was conductive or sensorineural.

Those patients with grossly abnormal responses to pure tone audiometry were tested by brain stem evoked response audiometry to identify the possible sites of the lesions. Patients were retested at six monthly intervals when possible. The Madsen OB 802 Clinical Audiometer was used for the pure tone audiometry and the Medelec ER 94A Sensor for the evoked response audiometry.

Serum ferritin concentrations were measured by an immunoradiometric assay, a modification of the method of Addison *et al*,[8] and plasma zinc and copper concentrations with a Perkin-Elmer model 306 atomic absorption spectrophotometer by a modification of the method of Scudder *et al*.[9] Urinary zinc was estimated by direct aspiration of urine into an air/acetylene flame of a Perkin-Elmer model 306 atomic absorption spectrophotometer. Urine specimens giving absorptions greater than 15 µmol/l were diluted 1:20, 1:50, or 1:100, as appropriate, and reaspirated. Caeruloplasmin concentrations were estimated by single radial immunodiffusion.[10] Commercially prepared NOR partigen immunodiffusion plates, lyophilised protein standards, and controls were obtained from Hoeschst UK. Serum magnesium concentrations were analysed with a Perkin-Elmer model 370 atomic absorption spectrophotometer by a modification of the method of Hansen and Freier.[11] Plasma calcium was analysed by a standard SMA-2 method (Technicon). Ca-DTPA was obtained from Astrapin Pharmaceutical Preparations and the MS-16 syringe driver from Graseby Dynamics.

Results

AUDIOMETRY

Thirteen of the evaluable patients (26%) showed hearing loss (at least one point on the audiogram below 30 decibels). The hearing loss showed three different patterns. A high tone dip was found in six of the patients (12%) (fig 1); all were asymptomatic. This is similar to the loss found in acoustic trauma, but none of these patients had been exposed to excessive noise. Two of the patients (4%), also asymptomatic, had low tone hearing loss (fig 2). Five patients (10%), all of whom were symptomatic had severe hearing loss (fig 2) that was most pronounced at high tones. One needed a hearing aid, another had difficulties at school, and the other three were aware of their problems and tried to compensate by sitting in the front rows at college. All five patients with severe hearing loss were receiving comparatively high doses of desferrioxamine (table 1), and four had normal or nearly normal serum ferritin concentrations (table 2). No appreciable abnormality other than a threshold shift was seen in these patients when they were tested by brain stem evoked audiometry, indicating that the lesions were probably in the cochlea rather than a more proximal position along the auditory pathway.

TREATMENT

Treatment with desferrioxamine was immediately stopped in the five symptomatic patients and replaced by Ca-DTPA. The dose of Ca-DTPA ranged

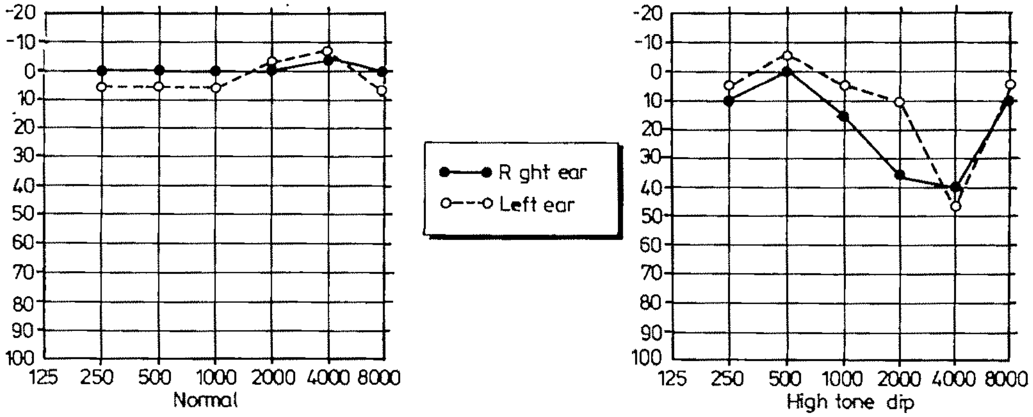


Fig 1 *On the left, normal audiogram; on the right audiogram typical of the six patients (12%) with high tone hearing loss.*

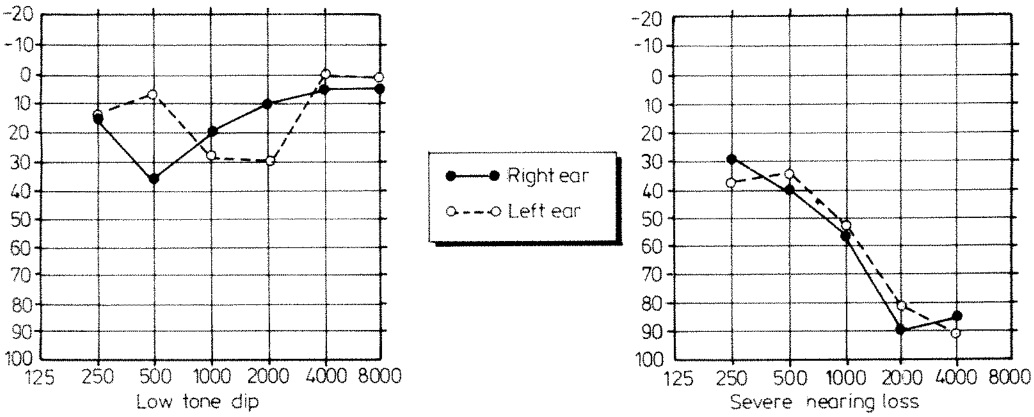


Fig 2 *On the left, typical audiogram of two of the patients with low tone hearing loss. On the right typical audiogram of the five patients with severe deafness and loss of hearing at all frequencies, most pronounced at high tone*

initially from 0·5 g (cases 4 and 5) to 1 g (cases 1, 2, and 3) given subcutaneously on alternate days. This was increased after two months in all cases to 1 g five nights each week and 1 g of Ca-DTPA/unit of blood transfused (table 2). Ca-DTPA was given subcutaneously by the infusion pump over a period of 10–12 hours. Zinc sulphate was given orally as 200 mg capsules or 220 mg effervescent tablets two to five times daily depending on the plasma zinc concentration.

Table 2 gives details of the serum ferritin concentrations in these patients before treatment with Ca-DTPA was started, and the mean and range of serum ferritin measured every two to three months during treatment with Ca-DTPA. The normal ranges are (men) 39–340 μg/l and (women) 14–148 μg/l. The serum ferritin concentrations tended to rise slightly on the initially low dose of Ca DTPA but fell to the concentrations recorded before treatment with Ca-DTPA when the frequency and dose of Ca-DTPA were increased. Urinary iron excretion in response to subcutaneous Ca-DTPA

Table 1 *Details of five patients with severe deafness at the beginning of treatment with Ca-DTPA*

Case No	*Sex*	*Age (years)*	*No of units transfused*	*Duration of desferrioxamine treatment (years)*	*Dose of desferrioxamine (mg/kg body weight)*
1	Male	20	302	8	60
2	Female	18	313	9	80
3	Female	17	297	7	85
4	Male	8	108	5	90
5	Male	5	63	3	160

Table 2 *Association between serum ferritin concentrations and treatment with Ca-DTPA*

Case	*Duration of treatment with Ca-DTPA (months)*	*Serum ferritin concentration (μg/l)*		
		Before treatment with Ca-DTPA	*During treatment with Ca-DTPA*	
		Mean	*Mean*	*(Range)*
1	7	1500	1540	(1300–2070)
2	8	380	400	(220–430)
3	9	646	760	(440–860)
4	12	180	340	(280–480)
5	19	400	800	(450–1100)

did not vary significantly over the period of treatment (table 3). All five patients had normal plasma zinc concentrations before starting on treatment with Ca-DTPA (table 4). Plasma zinc concentrations were low in patients 2, 3, and 5 in the first few months of treatment with Ca-DTPA. This was because the patients could not tolerate the zinc sulphate capsules, and was corrected by changing to the effervescent zinc sulphate tablets and temporarily increasing the dosage to five tablets daily. Urinary zinc excretion and plasma zinc concentrations increased substantially in these three patients when oral zinc supplementation was increased. Subsequently urinary and plasma zinc concentrations did not vary greatly among the five patients, with supplementation of two or three zinc sulphate capsules or tablets daily (table 4). Normal zinc concentrations are urine 4·5–9·0 μmol/24 hours, and plasma 11·5–17 μmol/l. There were no significant changes in plasma copper, caeruloplasmin, magnesium, or calcium concentrations during treatment with Ca-DTPA (unpublished observations).

All patients with severe hearing loss showed substantial improvement in hearing. One patient recovered completely after 19 months of treatment with Ca-DTPA (fig 3). Improvement was noticeable after three to four months on treatment in two other patients, the remaining three (including the patient mentioned above), making more gradual recoveries. In one patient the delay may have been caused by concomitant middle ear infection that required several courses of treatment with antibiotics.

Table 3 *Urinary iron excretion in response to treatment with Ca-DTPA*

Duration of treatment with Ca-DTPA (months)	*Urinary iron excretion (mg/24 hours)*				
	Case Nos				
	1	*2*	*3*	*4*	*5*
0 (Control)	0·51	0·43	0·76	0·07	0·07
1	4·0	6·3	3·7	3·4	3·4
2	6·4	7·4	4·9	4·10	2·1
3	18·6	19·8	10·4	8·4	6·9
4	25·0	26·6	10·2	8·0	*
5	20·8	24·0	*	7·4	5·6
6	17·7	34·4	7·0	7·6	6·7
7	25·1	*	6·0	8·5	*
8	*	29·3	*	6·7	5·6
9	*	*	10·0	7·6	5·6
10	*	*	*	6·6	7·3
11	*	*	*	7·1	5·7
12	*	*	*	8·6	5·3
19	*	*	*	*	6·5

*Not measured.

Discussion

Desferrioxamine is a remarkably non-toxic drug with few side effects despite the large doses needed over many years. There have been local reactions to the drug and few patients develop allergic manifestations, but in most cases desensitisation can be successfully undertaken.[12]

In recent years, however, high doses of desferrioxamine given intravenously or subcutaneously have sometimes caused reversible retinal abnormalities, including cone and rod dysfunction, night blindness, field defects, and dyschromatopsia.[5 6] Tinnitus and high frequency sensorineural hearing

Table 4 *Concentrations of zinc in urine (μmol/24 hours, and plasma (μmol/l) during treatment with Ca-DTPA*

Duration of treatment with Ca-DTPA (months)	*Case No* *1*		*2*		*3*		*4*		*5*	
	Urine	*Plasma*	*Urine*	*Plasma*	*Urine*	*Plasma*	*Urine*	*Plasma*	*Urine*	*Plasma*
0 (Before treatment with Ca-DTPA)	7·2	15·0	6·1	13·4	4·6	16·7	4·3	16·8	5·3	14·1
1	227	20·8	160	13·4	142	12·1	214	19·5	51	11·2
2	297	22·2	240	*	160	5·9	113	16·8	50	14·1
3	445	20·0	*	*	505	16·7	769	49·2	129	9·4
4	419	22·0	445	9·3	366	12·1	306	*	1002	27·5
5	438	*	520	7·9	*	11·1	220	*	233	13·4
6	769	22·1	*	17·9	340	11·7	*	48·4	167	*
7	425	*	720	18·9	*	19·4	*	*	*	*
8	*	*	465	17·9	264	12·7	197	*	270	*
9	*	*	*	*	320	12·0	*	25·4	333	23·5
10	*	*	*	*	*	*	200	*	267	14·6
12	*	*	*	*	*	*	230	23·7	287	13·6
18	*	*	*	*	*	*	*	*	266	13·6
19	*	*	*	*	*	*	*	*	*	12·8

*Not measured.

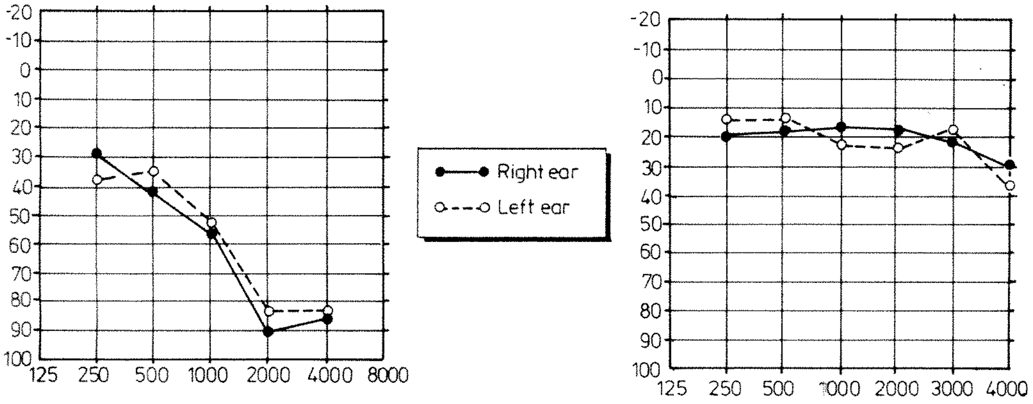


Fig 3 *Audiograms of case 5 before and after 19 months treatment with Ca-DTPA.*

deficits necessitating hearing aids have also occurred in some patients.[4,5] Audiometric assessment in the present group of 50 patients with homozygous β thalassaemia showed two patients with deafness and three patients with severe high frequency hearing loss; a further eight had mild asymptomatic hearing loss.

This incidence (26%) of hearing loss is remarkably high, as none of these abnormalities would be expected in a group of healthy normal children. High frequency hearing loss is a characteristic finding in patients receiving desferrioxamine[5] as well as other drugs—for example aminoglycosides. Although we cannot be certain it seems probable that the asymptomatic high tone 'dip' in six of our patients was caused by treatment with desferrioxamine. Mild 'low' tone hearing loss was also found in two patients, but the association of this with thalassaemia or treatment with desferrioxamine is not clear.

In all five severely affected patients treatment with desferrioxamine was stopped and replaced with Ca-DTPA. Ca-DTPA is as effective as desferrioxamine at inducing iron excretion.[13] Our results show that iron excretion is maintained during long term treatment with Ca-DTPA and serum ferritin concentrations also remained steady despite continued blood transfusions, suggesting that Ca-DTPA was as effective as desferrioxamine at causing iron excretion in the long term.

Other side effects of Ca-DTPA include chills, fever, nausea, vomiting, diarrhoea, pruritis, and muscle cramps.[14,15] Pippard *et al*[16] recently reviewed treatment with Ca-DTPA and found that if Ca-DTPA was given subcutaneously it was as effective as desferrioxamine at chelating iron. They suggested that the zinc depletion induced by Ca-DTPA could be prevented by giving oral zinc supplements. Our present results confirm this, as none of our patients developed the well recognised signs of zinc deficiency—diarrhoea, apathy, cutaneous lesions, or hair loss—and plasma zinc concentrations were maintained within normal limits over prolonged periods of treatment.

In these studies Ca-DTPA given subcutaneously was well tolerated. Local irritation and thickening of the subdermal tissues of the injection sites did not occur. Oral zinc supplements caused nausea and vomiting at first in three of the five patients, but these symptoms disappeared as treatment continued and the three patients were changed to effervescent tablets. It was then possible to maintain plasma zinc concentrations within normal limits in all five patients despite continued treatment with Ca-DTPA. Vitamin C supplements were not given as they do not seem to increase iron excretion with Ca-DTPA.[16]

We conclude that the auditory toxicity caused by desferrioxamine is reversible in at least a proportion of patients, that Ca-DTPA in the doses that we used does not cause side effects on the cochlea, and that Ca-DTPA may be used effectively and safely for long term iron chelation. Oral zinc supplements and regular estimations of trace elements, however, are clearly needed during treatment.

We thank the United Kingdom Thalassaemia Society for generous financial support (MA).

References

[1] Hussain MAM, Green N, Flynn DM, Hussein S, Hoffbrand AV. Subcutaneous infusion and intramuscular injection of desferrioxamine in patients with transfusional iron overload. *Lancet* 1976;**ii**:1278–80.

[2] Propper RD, Cooper B, Rufo RF, *et al.* Continuous subcutaneous administration of desferrioxamine in patients with iron overload. *N Engl J Med* 1977;**197**:418–23.

[3] Aldouri MA, Wonke B, Hoffbrand AV, *et al.* Iron state and hepatic disease in patients with thalassaemia major, treated with long term subcutaneous desferrioxamine. *J Clin Pathol* 1987;**40**:1353–9.

[4] Marsh MN, Clark C, Holbrook JC, Shaffer JL. Tinnitus in a patient with beta thalassaemia on long term treatment with desferrioxamine. *Postgrad Med J* 1981;**57**:582–4.

[5] Olivieri, NF, Buncic JR, Chew E, *et al.* Visual and auditory neurotoxicity in patients receiving subcutaneous desferrioxamine infusions. *N Engl J Med* 1986;**14**:869–73.

[6] Davies SC, Hungerford JL, Arden GB, Marcus RE, Miller MH, Huehns ER. Ocular toxicity of high dose intravenous desferrioxamine. *Lancet* 1983;**ii**:181–4.

[7] Rubinstein M, Dupont P, Doppee JP, Dehon C, Ducubu J, Hainaut J. Ocular toxicity of desferrioxamine. *Lancet* 1985; **i**:817–8.

[8] Addison GM, Beamish MR, Hales CN, Hodgkins M, Jacobs A, Llewellin P. An immunoradiometric assay for ferritin in the serum of normal subjects and patients with iron deficiency and iron overload. *J Clin Pathol* 1972;**25**:326–9.

[9] Scudder PR, Al-Timimi D, McMurray W, White AG, Zoob BC, Dormandy TL. Serum copper and related variables in rheumatoid arthritis. *Ann Rheum Dis* 1978;**37**:67–70.

[10] Marcini G, Carbonara AO, Heremans JF. Immunochemical quantitation of antigens by single radial immunodiffusion. *Immunochemistry* 1985;**2**:235–42.

[11] Hansen JL, Freier EF. The measurement of serum magnesium by atomic absorption spectrophotometry. *American Journal of Medical Technology* 1967;**3**:158–66.

[12] Miller KB, Rosenwasser, LJ, Bessette JM, Beer DJ, Rocklin RE. Rapid desensitisation for desferrioxamine anaphylactic reaction. *Lancet* 1981;**ii**:1059.

[13] Smith RS. Chelating agents in the diagnosis and treatment of iron overload in thalassaemia. *Ann N Y Acad Sci* 1964;**119**:776–88.

[14] Graziano JH, Cerami A. Chelation therapy for the treatment of thalassaemia. *Semin Hematol* 1977;**14**:127–34.

[15] Constantoulakis M, Economidou J, Karagiorga M, Katsanton A, Gyftaki E. Combined long term treatment of haemosiderosis with desferrioxamine and DTPA in homozygous beta thalassaemia. *Ann NY Acad Sci* 1974;**232**:193–200.

[16] Pippard MJ, Jackson MJ, Hoffman K, Petrou M, Modell CB. Iron chelation using subcutaneous infusions of diethylene triamine penta-acetic acid (DTPA). *Scand J Haematol* 1986;**36**:466–472.

Correspondence to Professor AV Hoffbrand, Department of Haematology, Royal Free Hospital, Pond Street, Hampstead, London NW3 2QG.

Accepted 26 July 1988

Archives of Disease in Childhood, 1989, **64,** 83–86

The 'happy puppet' syndrome of Angelman: review of the clinical features

S A ROBB, K R E POHL, M BARAITSER, J WILSON, AND E M BRETT
Hospital for Sick Children, Great Ormond Street, London

SUMMARY Thirty six children with typical features of Angelman's syndrome, including global developmental delay, ataxia, episodes of paroxysmal laughter, seizures, and microcephaly were studied. The series included three sibships of three affected sisters, two affected brothers, and two affected sisters, respectively. The facial appearance is characterised by a prominent jaw, a wide mouth, and a pointed chin. Tongue thrusting is common. The movement disorder consists of a wide based, ataxic gait with frequent jerky limb movements and flapping of the hands. Tone is variable in the limbs with normal reflexes, and the plantar responses are usually flexor. The syndrome is being diagnosed more often, and attention is drawn to its diagnostic aspects.

In 1965 Angelman described a disorder affecting three unrelated, mentally subnormal children who had strikingly similar appearances, with unusual jerking movements, brachycephaly, protruding tongues, episodes of unprovoked laughter, and seizures.[1] He remarked on the resemblance of this picture to that of a marionette and used the term 'puppet children' to describe the syndrome. Bower and Jeavons,[2] describing two similar children, emphasised their happy demeanour and suggested that 'happy puppet' more aptly described the disorder. Further case reports followed,[3-8] but their sporadic nature and small numbers suggested a rare syndrome. Though Williams and Frias suggested that the incidence may have been underestimated,[9] fewer than 50 cases have so far been reported.

Since 1981 when Pampiglione[10] drew attention to a number of unusual electroencephalographic features that had previously been described by Bower and Jeavons,[2] we have identified 36 patients suffering from Angelman's syndrome at the Hospital for Sick Children, although the diagnosis was usually not made before referral. The correct diagnosis has assumed greater importance with the recent reports of familial cases[11-14] suggesting that—rather than being sporadic—the syndrome may have genetic implications.

This report reviews the clinical features at diagnosis of our cases of Angelman's syndrome and by including three sets of siblings stresses the importance of genetic counselling.

Patients and diagnostic criteria

All patients fulfilled the following diagnostic criteria: delayed developmental milestones from early infancy; jerky ataxia; head circumference below the 50th centile for age; typical facial features with prominent lower jaw, wide mouth, and frequent tongue thrusting; happy disposition, often with episodes of paroxysmal or unprovoked laughter; and electroencephalographic features as described by Boyd *et al.*[15]

Most of the patients had had seizures by the time of presentation, but these were not a prerequisite for the diagnosis. Thirty five of the patients were white and one was of east African Asian parentage. None of the parents was consanguineous. All patients were referred to the Departments of Neurology or Genetics at the Hospital for Sick Children for investigation of unexplained neurodevelopmental delay.

Results

The series comprised 18 boys and 18 girls aged between 18 months and 13 years 6 months at the time of diagnosis. There were three sets of siblings (three girls, two boys, and two girls); two sibling pairs have previously been reported.[13] Pregnancy and delivery had usually been normal, with a mean birth weight for the group of 3060 g. Subsequent growth had usually been normal; there was one boy

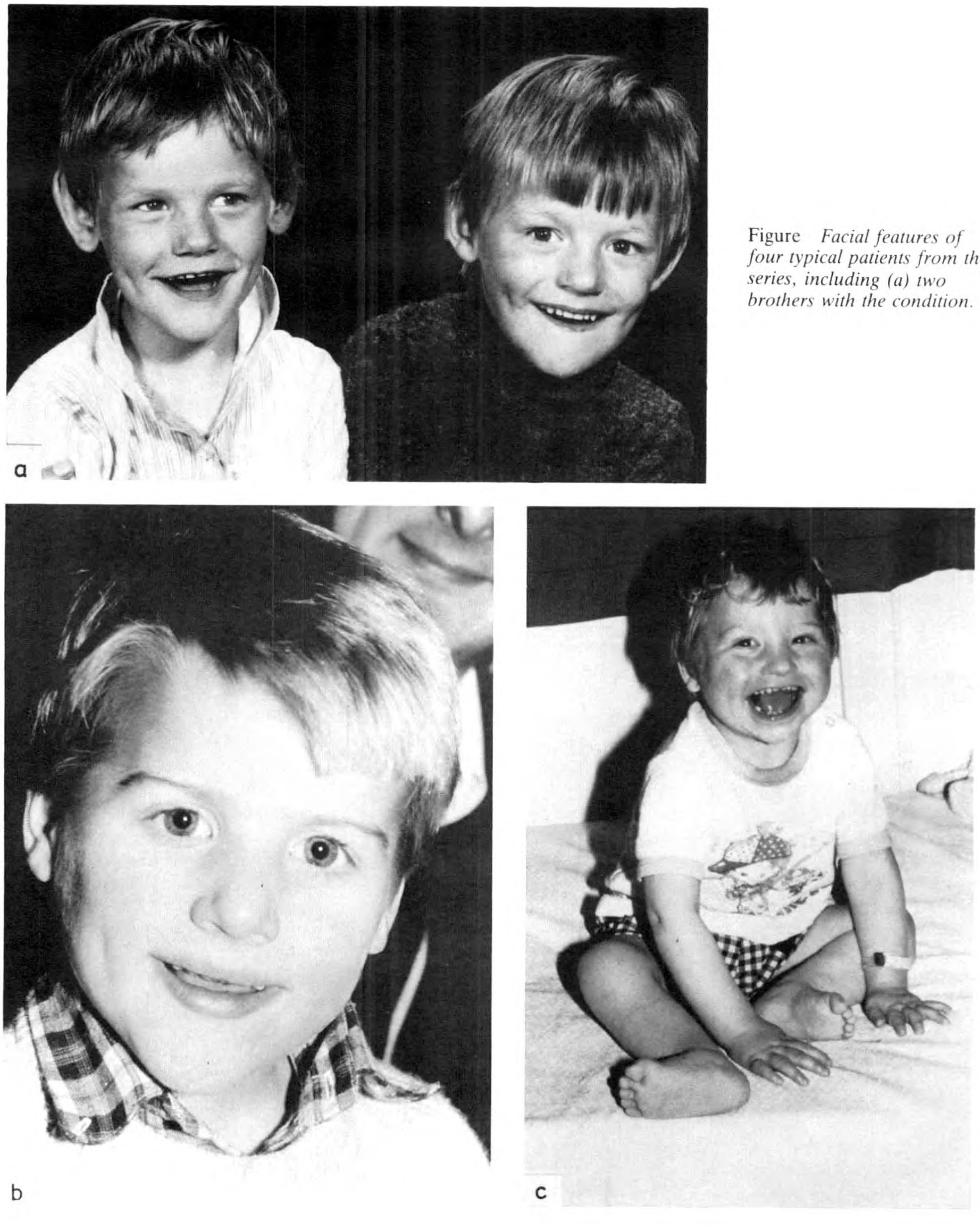


Figure *Facial features of four typical patients from the series, including (a) two brothers with the condition.*

aged 3 years 1 month whose height and weight were just below the third centile for no obvious reason. All children had delayed developmental milestones noted from infancy.

FACIAL FEATURES

The facial features though not pathognomic are highly suggestive, and are summarised in the table and shown in the figure. All patients had wide mouths, wide lower faces, rather prominent jaws, and pointed chins. Most had thin upper lips and bowed upper dentition that may have been caused by the frequent tongue thrusting.

Though most reports have stressed that these children have blonde hair and blue eyes, one third of our series were dark. Episodes of paroxysmal laughter are common, but may not always occur in infancy; some of our children (notably one child with severe gastro-oesophageal reflux) were miserable and difficult to manage as infants.

Table *Main clinical features in 36 children with Angelman's syndrome*

	No of patients
Sex:	
Male	18
Female	18
Mental retardation	36
Facial features:	
Wide mouth	36
Wide lower face	36
Prominent jaw	36
Pointed chin	36
Thin upper lip	32
Bowed teeth	19
Colouring:	
Blonde or red hair with blue eyes	24
Other	12
Head circumference:	
Below second centile	25
Second to 50th centile	11
Seizures	28
Jerky ataxia	36
Walking:	
Total	25
Unaided	18
Hands held	7
Speech:	
Less than three words	7
More than three words	0
Muscle tone:	
Decreased	7
Increased	11
Normal	18
Tendon reflexes:	
Normal	36
Abnormal	0
Plantar responses:	
Normal	34
Equivocal	2
Computed tomography:	
Normal	15 (of 23)
Showed mild atrophy	8 (of 23)
Electroencephalogram abnormal	36

AGE AT DIAGNOSIS

There may be an evolution of facial features (as seen from earlier family photographs) so that below the age of one year (when the movement disorder is less obvious) clinical diagnosis may be difficult. The youngest age at diagnosis was 18 months. Twenty one cases (58%) were diagnosed before the age of 5 years (median 2–3 years).

SEIZURES

Seizures were present at the time of diagnosis in 28 patients (78%). The mean age of onset was 2 years, but most (26, 93%) had developed seizures by the age of 4 years. Of the eight patients who had not had seizures at the time of diagnosis, seven were aged 25 months or less; the remaining patient, a girl aged 13 years 6 months, fulfilled all other diagnostic criteria and also has a sister with Angelman's syndrome who had seizures.

MENTAL HANDICAP

All patients were severely mentally handicapped, with a particularly profound language deficit. Only seven patients could speak any words at all, and the maximum number was three.

MOVEMENT DISORDER

The movement disorder, present in all, consisted of a jerky ataxia affecting all limbs with a wide based gait and frequent flapping of the hands. Most children learned to walk though this was delayed, the earliest age at walking being 19 months. Twenty five patients (69%) could walk at the time of diagnosis, most having walked between the ages of 2 and 3 years; of the 11 children who could not walk, six were still less than 2 years old and may walk later.

NEUROLOGICAL SIGNS

Twenty five of the patients (69%) were microcephalic (head circumference below the second centile), and of the remainder none had a head circumference above the 50th centile for age. Muscle tone was variable being normal or slightly decreased below the age of 3 years; limb tone was mildly increased in 11 children, 10 of whom were aged over 3 years. Tendon reflexes were brisk in these children, but normal in the rest. Plantar responses were flexor in 34 and equivocal in two.

INVESTIGATIONS

The electroencephalograms were abnormal in all patients, the abnormalities consisting of generalised, rather rhythmic intermediate slow waves at 4–6 cycles/second (c/s) and runs of 2–3 c/s activity anteriorly often with discharges. On closure of the eyes spikes with 2–4 c/s activity were seen posteriorly. Details of these changes are described elsewhere.[15] Computed tomography of the brain was normal in 15 of the 23 patients examined and showed mild cerebral atrophy in eight. One of the scans also showed a small left temporal arachnoid cyst that was not considered to be of clinical importance.

The results of biochemical screening (including estimations of renal and hepatic function, and plasma ammonia and amino acid, urine amino acid, and organic acid concentrations) were normal, as were haematological measurements. After an interstitial deletion of 15q11–13 was detected in one child, reassessment of chromosome preparations from 10 further children showed four similar deletions.[16]

Conclusion

The aim of this report was to draw attention to the diagnostic features of Angelman's syndrome, which may be recognised in children presenting with unexplained neurodevelopmental delay, and to point out that this condition (when specifically looked for) is commoner than has been hitherto thought. The combination of the facial features, profound retardation, ataxic movement disorder, seizures, and happy disposition strongly suggests the diagnosis and this may be confirmed by electroencephalographic analysis. The reports of familial cases both in this series and in other publications[1–14] highlight the need for accurate recognition of the syndrome in order to be able to discuss the prognosis and management and to refer the parents for appropriate genetic counselling.

We thank Drs Ann Harden and Stewart Boyd for providing electroencephalographic data on the patients, and Dr Brian Kendall for reviewing the computed tomograms.

References

[1] Angelman H. 'Puppet' children, a report on three cases. *Dev Med Child Neurol* 1965;**7**:681–8.

[2] Bower BD, Jeavons PM. The 'happy puppet' syndrome. *Arch Dis Child* 1967;**42**:298–302.

[3] Berg JM, Pakula Z. Angelman's ('happy puppet') syndrome. *Am J Dis Child* 1972;**123**:72–4.

[4] Mayo O, Nelson OM, Townsend HRA. Three more 'happy puppets'. *Dev Med Child Neurol* 1973;**15**:63–74.

[5] Moore JR, Jeavons PM. The 'happy puppet' syndrome: two new cases and a review of previous cases. *Neuropadiatrie* 1973;**4**: 172–9.

[6] Elian M. Fourteen happy puppets. *Clin Pediatr* 1975;**14**:902–8.

[7] Dooley JM, Berg JM, Pakula Z, MacGregor DL. The puppet-like syndrome of Angelman. *Am J Dis Child* 1981;**135**:621–4.

[8] Hersh JA, Bloom AS, Zimmerman AW, *et al.* Behavioural correlates in the happy puppet syndrome: a characteristic profile? *Dev Med Child Neurol* 1981;**23**:792–800.

[9] Williams CA, Frias JL. The Angelman ('happy puppet') syndrome. *Am J Med Genet* 1982;**11**:453–60.

[10] Pampiglione G, Martinez A. Evolution of Angelman syndrome. Follow up of three new cases. *Electroencephalogr Clin Neurophysiol* 1983;**56**:72P.

[11] Kurohi Y, Matsui I, Yamamoto Y. The 'happy puppet' syndrome in two siblings. *Hum Genet* 1982;**56**:227–9.

[12] Pashayan HM, Singer W, Bove C, Eisenberg E, Seto B. The Angelman syndrome in two brothers. *Am J Med Genet* 1982;**13**:295–8.

[13] Baraitser M, Patton MA, Lam STS, Brett EM, Wilson J. The Angelman (happy puppet) syndrome: is it autosomal recessive? *Clin Genet* 1987;**31**:323–30.

[14] Fisher JA, Burn J, Alexander FW, Gardner-Medwin D. Angelman (happy puppet) syndrome in a girl and her brother. *J Med Genet* 1987;**24**:294–8.

[15] Boyd SG, Harden A, Patton MA. The EEG in early diagnosis of Angelman's (happy puppet) syndrome. *Eur J Ped* 1988;**147**: 503–13.

[16] Pembrey M, Fennell J, van den Berghe J, *et al.* The association of Angelman syndrome and deletions within 15q11–13. *J Med Genet* 1988;**25**:274.

Correspondence to Dr SA Robb, Department of Neurology, Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

Accepted 25 February 1988

Archives of Disease in Childhood, 1989, **64,** 87–91

Acute gastroenteritis in well nourished infants: comparison of four feeding regimens

S P CONWAY* AND A IRESON†

*Departments of *Infectious Disease and †Dietetics, Seacroft Hospital, Leeds*

SUMMARY Two hundred well hydrated babies of 6 weeks to 12 months of age who had been fed on formula feeds and who were admitted with acute gastroenteritis were randomly allocated to receive either a standard return to full milk feeds, or immediate full strength feeds with one of three milk formulas, HN25, SMA Gold Cap, or Formula S. There were significant differences in weight change among the four treatment groups at two and five days, with initial weight loss recorded only for the group of babies who were receiving the graded return to full feeding. There was no difference in the duration of diarrhoea after admission, nor in the time to discharge. Eighteen babies were classified as failures of treatment. None had long term complications. Well hydrated infants with acute gastroenteritis may resume full milk feeding immediately.

Acute gastroenteritis is an important cause of morbidity among infants in Britain.[1 2] Optimum nutritional management of these children is controversial.[3] In 1948 Chung showed better weight gain, larger and more solid stools, effective absorption of all food elements, and no increase in the duration of diarrhoea in infants with acute gastroenteritis treated with early full feeding.[4 5] Malnourished children with repeated attacks of acute gastroenteritis may enter a cycle of protein energy/fluid electrolyte malnutrition induced by periods of enforced starvation during treatment. Early rapid and full refeeding can interrupt this cycle without causing any deterioration in the diarrhoeal illness,[6] by preventing the fall in intestinal mucosal disaccharidase activity associated with fasting[7] and potentially helping to maintain the integrity of the intestinal mucosa.[3] None the less, many well nourished, well hydrated infants in the developed world are still fed on oral glucose electrolyte solutions for at least the first 24 to 48 hours of their diarrhoeal illness. Formula milks and other foods are then introduced gradually over periods of two to five days. A more rapid return to full feeds for older children is now recommended by some, but caution is still advised for infants less than 6 months old.[9]

Theoretically delayed feeding may avoid the complications of carbohydrate malabsorption, of increased fluid loss and systemic acidosis, and of food intolerance resulting from the absorption of whole protein by the damaged mucosa.[3] In practice the incidence of carbohydrate malabsorption associated with acute infantile gastroenteritis has been falling since the introduction of low solute formula feeds.[10] These are as effective as hypoallergenic formulas in preventing sensitisation to cows' milk protein.[11]

The purpose of this study was to compare rapid refeeding with either a standard cows' milk formula feed (SMA Gold Cap), a low lactose formula (HN25), or a soya based milk (Formula S) with a period of fasting followed by a gradual reintroduction of full strength feeds, in the treatment of acute gastroenteritis in well nourished infants.

Patients and methods

Two hundred consecutive babies aged 6 weeks to 12 months, who had been fed on formula feeds and who were admitted with acute gastroenteritis (defined as the acute onset of watery or extremely loose stools with or without vomiting of 14 days duration or less and without infection outside the gastrointestinal tract or other illness) were entered into the study from July 1986 to February 1987.

Each infant was randomised to one of four treatment regimens. Group 1 received 24 hours of oral rehydration solution (Dextrolyte, Cow and Gate), followed by 24 hours of half strength and 24 hours of three quarter strength SMA Gold Cap (Wyeth) before continued feeding with the full

P24932

strength formula milk. Group 2 received special formula HN25 feed (Milupa) until two days after the stools returned to normal followed—on successive days—by replacement of one, three, and then all HN25 feeds by full strength SMA Gold Cap. Group 3 continued feeding with full strength SMA Gold Cap from the time of admission, and group 4 continued feeding with Formula S (Cow and Gate) from the time of admission.

Dextrolyte is a prepacked oral rehydration solution containing sodium 35 mmol/l, potassium 13·4 mmol/l, chloride 30·5 mmol/l, lactate 17·7 mmol/l, and glucose 200 mmol/l. HN25 is a low lactose feed with a reduced fat content (table 1).

On admission details of the severity and duration of diarrhoea and of any treatment already received were noted. The degree of dehydration was assessed as absent, 2·5–5%, 5–10%, or 10–15%.[12] All dehydrated infants were first rehydrated with Dextrolyte or intravenous fluids before receiving their assigned feeding regimen. The infants in group 1 then received a further 24 hours oral rehydration solution as the first stage in their return to full strength feed. Baby rice was given to those infants who routinely received solids to eliminate the possibility of a variety of solids influencing results. All infants were weighed on admission and the percentage weight change noted on days two and five, and at discharge.

All intake, and stool output and quality, were noted by nursing staff. Stools were described as constipated, normal soft, curdy, loose, or watery. The duration of diarrhoea was defined as 24 hours after the last fluid stool, and the severity of diarrhoea as the number of watery or loose stools each day until the diarrhoea stopped. Failure of treatment was defined as continued or increased severity of diarrhoea with weight loss or deteriorating fluid-electrolyte imbalance, or both. These children were treated with oral rehydration solution or intravenous fluids, or both, and with a gradual reintroduction of formula milk according to the standard regimen used in this hospital. If there was a further relapse, a soya or hydrolysed casein formula milk (Formula S or Nutramigen) was substituted. Stool specimens were examined for *Salmonella* and *Shigella* (desoxycholate citrate agar), *Campylobacter* (Skirrow's medium), *Escherichia coli* (MacConkey's agar), *Cryptosporidia* (auramine carbol fuchsin stain), and for rotaviruses (enzyme immunoassay).

The study was approved by the hospital ethical committee and fully informed verbal parental consent obtained in all cases. The significance of differences was assessed by the χ^2 test, one way analysis of variance, contingency table analysis, and multiple regression analysis.

Results

The characteristics of the 200 babies on admission are shown in table 2. One way analyses of variance or contingency table analysis, as appropriate, indicated no significant differences in admission characteristics among the groups. Three babies in each of groups 1 and 2, and four babies in each of groups 3 and 4, were mildly dehydrated (2·5–5%). One baby in group 1, three in group 2, and two in group 3 were moderately dehydrated (5–10%); All the other babies were clinically well hydrated. Only nine babies were below the third centile for weight.

One way analysis of variance showed significant differences in weight change at 48 hours among the four feeding regimens (p=0·01). Group 1 babies lost weight, and groups 2, 3, and 4 gained weight, the greatest change being in babies in group 2. These changes remained significant at five days (p=0·05)

Table 1 *Composition of infant feeding formulas*

	*HN25**	*SMA Gold Cap*	*Formula S*	*DHSS guidelines for nutrient content/100 ml*
†Main protein source (content/100 ml)	Cows' milk (2·5 g)	Cows' milk (1·5 g)	Soya protein isolate (1·8 g)	1·2–2·0 g
Fat source (content/100 ml)	Vegetable (1·2 g)	Beef and vegetable (3·6 g)	Vegetable (3·6 g)	2·3–5·0 g
Carbohydrate source (content/100 ml)	Banana, rice, cornflour, malto-dextrin (9·5 g)	Lactose (7·2 g)	Glucose syrup (6·7 g)	4·8–10·0 g
Energy kJ/100 ml	242·7	272·0	280·3	272·0–313·8

*Maximum recommended period as sole source of nourishment is 7 to 10 days.

†Specific information on the small amount of protein in HN25 contributed by the banana, rice, and cornflour is not available from the manufacturer.

Table 2 *Admission characteristics of study groups. Figures are given as mean (SD)*

	Group 1	*Group 2*	*Group 3*	*Group 4*
Weight (kg)	6·2 (1·5)	6·5 (1·6)	6·26 (1·8)	6·5 (1·4)
Age (months)	4·5 (2·6)	5·5 (2·5)	4·9 (2·9)	4·9 (2·4)
Duration of diarrhoea (days)	5·0 (3·6)	4·9 (3·7)	5·5 (3·3)	4·3 (3·3)
No of diarrhoeal stools/day	5·7 (2·7)	6·5 (3·9)	7·0 (4·3)	6·7 (3·7)
Packed cell volume	·037 (·027)	·034 (·035)	·034 (·042)	·034 (·037)
Plasma sodium concentration (mmol/l)	139 (2·9)	139 (2·9)	139 (2·7)	139 (4·4)
Plasma potassium concentration (mmol/l)	4·6 (0·5)	4·6 (0·4)	4·6 (0·7)	4·6 (0·53)
Plasma chloride concentration (mmol/l)	105 (4·2)	106 (4·0)	106 (4·4)	106 (4·5)
Plasma bicarbonate concentration (mmol/l)	20 (3·2)	19 (3·1)	19 (3·8)	20 (3·1)
Plasma urea concentration (mmol/l)	3·2 (2·1)	3·4 (1·8)	3·5 (2·5)	3·7 (3·9)
Plasma creatinine concentration (µmol/l)	37 (9·8)	40 (15)	41 (18·7)	38 (14·8)
Treatment with oral rehydration solution before admission	32 of 50	29 of 50	27 of 50	29 of 50

There were no significant differences.

but had virtually disappeared by the time of discharge when the differences were no longer significant (figure).

The factors affecting the weight gain after two days in hospital were further examined by a multiple regression analysis of the gain on the admission variables and on the feeding regimen. The coefficient for the effect of intravenous rehydration is significant (p=0·05) and this implies that intravenous rehydration results in weight gains of up to 2% more when compared with those not requiring intravenous fluids. One baby in group 1 received intravenous fluid replacement for 38 hours after admission, three babies in group 2 for 25, 26, and 40 hours, respectively, two babies in group 3 for 21 and 68 hours, respectively, and two babies in group 4 for 38 and 60 hours, respectively. These differences are not significant. A mean period of 12 hours (range four to 24) was taken for oral rehydration with Dextrolyte.

Differences between the groups in the severity of diarrhoea after admission were significant (p=0·05) being less in group 2 (mean (SD) 0·8 (1·7) diarrhoeal stools a day) than in group 3 (1·8 (1·5) a day), with group 4 (1·4 (1·9) and group 1 (1·6 (1·7)) occupying intermediate positions. There was no significant difference among the four treatment groups in the duration of diarrhoea after admission, the mean (SD) times being 64 (53·7), 47 (53·7), 68 (43·6), and 51 (41·5) hours, respectively, nor in the times to discharge, which were 6·9 (3·2), 6·9 (1·9), 6·9 (2·2), and 7·1 (3·6) days, respectively. Details of the gut pathogens identified in the infants' stools are shown in table 3.

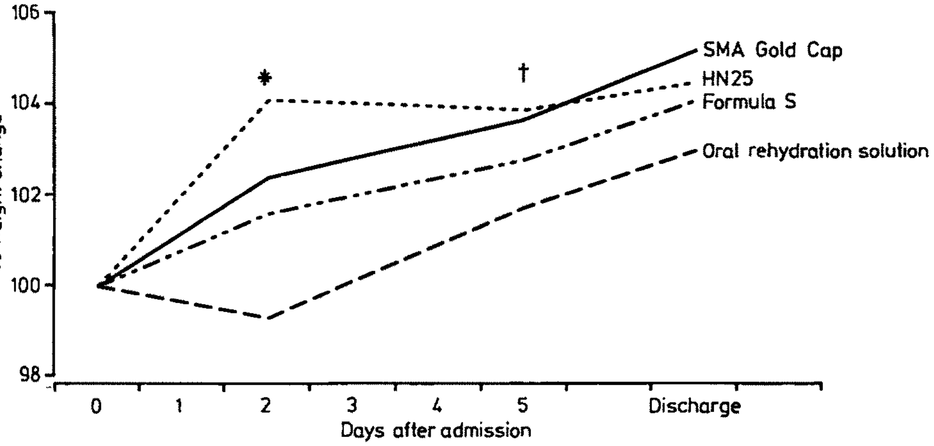


Figure *Percentage weight change at day 2 (*p=0·01), day 5 (†p=0·05), and discharge (NS).*

Table 3 *Results of stool examination for gut pathogens*

	Group 1	*Group 2*	*Group 3*	*Group 4*
No agent identified	34	37	30	28
Rotavirus	12	9	11	13
Salmonella spp	3	1	3	6
Campylobacter	0	1	1	2
Escherichia coli	0	2	4	1
Rotavirus and *E coli*	1	0	0	0
Rotavirus, *Salmonella* spp, and *E coli*	0	0	1	0
Total	50	50	50	50

Two babies in group 1 (one who had rotavirus and one in whom no pathogen was identified), eight babies in group 2 (one who had *Salmonella* sp, one who had rotavirus, and six in whom no pathogen was identified), four babies in group three (one who had *Salmonella* species, two who had rotavirus, and one in whom no pathogen was identified), and four babies in group 4 (one who had *Salmonella* sp, one who had *E Coli*, and two in whom no pathogen was identified), were designated failures of treatment. There is no evidence that the probability of failure of treatment differed among the groups. It may be concluded that the observed differences are random effects.

One of the two failures in group 1 settled with a second standard return to normal feeding, the other on Formula S. Of the eight failures in group 2 six tolerated the HN25 well and relapsed only on the introduction of SMA Gold Cap. All of these failed a second return to normal feeding but settled when given Formula S or Nutramigen. One baby in group 2 was withdrawn from the trial because of early vomiting. This continued when he was given Dextrolyte, and in retrospect was probably a relection of his rotavirus infection. The remaining failure in group 2 was withdrawn because of continued diarrhoea and weight loss (200 g in five days). *Salmonella Worthington* was isolated from the stools. Moderate diarrhoea continued during return to normal feeding, the child being discharged thriving but with persistent watery stools at 10 days. Three failures in group 3 settled the second time a return to normal feeding was attempted, and one required Nutramigen. Three failures in group 4 continued with profuse diarrhoea despite oral rehydration solution, and required intravenous fluid replacement. One failure in group 4 with a history of atopy settled only when given Nutramigen. Allergy to cows' milk or soya were presumed to account for most of the failures of treatment. In our opinion no baby had persistent diarrheoa severe enough to warrant a small bowel biopsy. Only three failures of treatment required intravenous fluids (4% dextrose and 0·18% sodium chloride) for 32, 38, and 44 hours, respectively. Three, 10, and three stools, respectively were passed during the period of intravenous treatment and on discontinuation of this the infants were tolerating full strength feeds within 33, 80, and 28 hours without any subsequent relapse.

These 18 babies did not differ significantly from those successfully treated in weight or age at admission, in duration or severity of diarrhoea, in packed cell volume, or plasma sodium, potassium, chloride, bicarbonate, urea or creatinine concentrations. None of the babies was dehydrated on admission.

One hundred and seventeen babies received treatment with an oral rehydration solution before admission. Four of the 18 failures of treatment occurred in this group and 14 in the 83 babies who had received no oral rehydration solution. Contingency table analysis indicated significant differences in these proportions of failures (p=0·001).

Discussion

The continuation of breast feeding is routinely recommended in breast fed infants with acute gastroenteritis[3] and has been shown to be of clinical benefit when compared with the use of oral rehydration solution alone.[13] It is illogical to advocate continued breast feeding on the one hand, and a period of fasting and diluted cows' milk formula for non-breast fed infants on the other. Recent studies have substantiated the early work of Chung in confirming the safety and benefits of early refeeding in acute gastroenteritis of childhood.[14 15] Reservations have been expressed concerning rapid refeeding in early infancy[15 16] although delayed recovery seems to be restricted to infants who are both young and malnourished.[11 17]

It is probably essential for an infant to be well hydrated for rapid refeeding to be successful, so that the dangers of prolonged acidosis and protracted vomiting are avoided.[18] We have shown that well nourished, well hydrated infants, most with acute mild gastroenteritis, have no need for a gradual return to normal feeding. Those infants allocated to a rapid refeeding regimen showed better early weight gain with no increase in the duration of diarrhoea or in the time spent in hospital. All four feeding regimens were well tolerated. There were no long term complications in any of the 18 infants who failed to respond to treatment.

In northern Europe there is widespread acknowledgment of the decreasing incidence of lactose intolerance,[11 16] which is probably largely a secondary manifestation of cows' milk protein intolerance.[19] The results of a study of a non-hospital based, less selected population suggest that there is no need for routine use of a non-lactose formula in the treatment of mild acute gastroenteritis.[20] Moreover, documented lactose intolerance invariably responds rapidly to temporary omission of lactose from the diet.[21] Our results show better early weight gain in group 2 (HN25), and less severe diarrhoea in groups 2 (HN25) and 4 (Formula S), but no difference in either the duration of diarrhoea or in time to discharge when compared with group 3 (SMA Gold Cap). Modern adapted low solute cows' milk formula feeds are at least as effective as a hypoallergenic feeding formula (Pregestimil) in preventing sensitisation of the gut.[11] Our study confirms the safety of rapid refeeding with a standard formula feed.

One hundred and seventeen of our 200 infants had received oral rehydration solution before admission, and thus it is not possible to extrapolate from our results to discussion of the safety and benefits of continued feeding, as opposed to rapid refeeding, in acute infantile diarrhoea. It is significant ($p=0{\cdot}001$) that 14 of the 18 failures of treatment had not received treatment with an oral rehydration solution before admission. This may be attributed to the beneficial effects of the early treatment or alternatively could imply that general practitioners are themselves less likely to treat cases where the expectation of success is judged to be low. None the less, 53 (82%) of 65 babies who received no oral rehydration solution before admission and who were subsequently allocated to groups 2, 3, or 4 settled well on a continued feeding regimen. A cautious interpretation of our results, however, necessitates a 24 hour period of treatment with an oral rehydration solution before the resumption of full milk feeds.

Patients who fail to respond to this regimen may be given a further 24 hour period of oral rehydration solution followed by a standard return to normal feeding or rapid feeding with either a soya based or hydrolysed casein formula milk. Whenever a special formula milk is used, return to normal feeding should be supervised. Infants with acute gastroenteritis without signs of clinical dehydration, or after rehydration with an oral rehydration solution or intravenous fluids, need have little disturbance in their normal dietary intake. Full milk feeding may be resumed immediately with a rapid reintroduction of solids where indicated.

We thank Dr J Stevenson and Dr H Pullen for permission to study their patients and for encouragement and advice, Dr A Baines for the statistical analysis, and the nursing staff for their support.

References

[1] Pullan CR, Dellagrammatikas H, Steiner H. Survey of gastroenteritis in children admitted to hospital in Newcastle upon Tyne in 1971–5. *Br Med J* 1977;i:619–21.
[2] Isaacs D, Day D, Crook S. Childhood gastroenteritis: a population study. *Br Med J* 1986;**293**:545–6.
[3] Brown KH, MacLean WC. Nutritional management of acute diarrhoea: an appraisal of the alternatives. *Pediatrics* 1984;**73**:119–25.
[4] Chung AW. The effect of oral feeding at different levels on the absorption of foodstuffs in infantile diarrhoea. *J Pediatr* 1948;**33**:1–13.
[5] Chung AW, Viscorova B. The effect of early oral feeding versus early oral starvation on the course of infantile diarrhoea. *J Pediatr* 1948;**33**:14–22.
[6] Soeprapto, Soenarto Y, Nelwan, Meoenginah PA, Ismangoen. Feeding children with diarrhoea. *Trop Pediatr Environ Child Health* 1979;**25**:97–100.
[7] Knudsen KB, Bradley EM, Lecocq FR, Bellamy HM, Welsh J. Effect of fasting and refeeding on the histology and disaccharidase activity of the human intestine. *Gastroenterology* 1968;**55**:46–51.
[8] Wharton BA. Gastroenteritis in Britain: management at home. *Br Med J* 1981;**283**:1277–8.
[9] Wharton BA, Pugh RE, Taitz LS, Walker-Smith JA, Booth IW. Dietary management of gastroenteritis in Britain. *Br Med J* 1988;**296**:450–2.
[10] Anonymous. What has happened to carbohydrate intolerance following gastroenteritis? *Lancet* 1987;**i**:23–4.
[11] Manuel PD, Walker-Smith JA. A comparison of three infant feeding formulae for the prevention of delayed recovery after infantile gastroenteritis. *Acta Pediatrica Belgia* 1981;**34**:13–20.
[12] Ironside AG, Tuxford AF, Heyworth B. A survey of infantile gastroenteritis. *Br Med J* 1970;**iii**:20–4.
[13] Khin-Maung-U, Nyunt-Nyunt-Wai, Myo-Khin, Mu-Mu-Khin, Tin-U, Thane-Toe. Effect on clinical outcome of breast feeding during acute diarrhoea. *Br Med J* 1985;**290**:587–9.
[14] Rees L, Brook CGD. Gradual reintroduction of full strength milk after acute gastroenteritis in children. *Lancet* 1979;**i**:770–1.
[15] Dugdale A, Lovell S, Cribbs V, Ball D. Refeeding after acute gastroenteritis: a controlled study. *Arch Dis Child* 1982;**57**:76–8.
[16] Isolauri E, Vesikari T, Saha P, Viander M. Milk versus no milk in rapid refeeding after acute gastroenteritis. *J Pediatr Gastroenterol Nutr* 1986;**5**:254–61.
[17] Placzek M, Walker-Smith JA. Comparison of two feeding regimens following acute gastroenteritis in infancy. *J Pediatr Gastroenterol Nutr* 1984;**3**:245–8.
[18] Isolauri E, Vesikari T. Oral rehydration, rapid feeding, and cholestyramine for treatment of acute diarrhoea. *J Pediatr Gastroenterol Nutr* 1985;**4**:366–74.
[19] Walker-Smith JA. Cow's milk intolerance as a cause of postenteritis diarrhoea. *J Pediatr Gastroenteral Nutr* 1982;**1**:163–73.
[20] Groothuis JR, Berman S, Chapman J. Effect of carbohydrate ingested on outcome in infants with mild gastroenteritis. *J Pediatr* 1986;**108**:903–6.
[21] Davidson GP, Goodwin D, Robb TA. Incidence and duration of lactose malabsorption in children hospitalised with acute enteritis: a study in a well nourished urban population. *J Pediatr* 1984;**105**:587–90.

Correspondence to Dr SP Conway, Department of Infectious Disease, Seacroft Hospital, York Road, Leeds, LS14 6UH.

Accepted 9 August 1988

Archives of Disease in Childhood, 1989, **64,** 92–95

Production of interferon in respiratory syncytial virus bronchiolitis

D ISAACS

Infectious Disease Unit, Department of Paediatrics, John Radcliffe Hospital, Oxford

SUMMARY Production of interferon alfa in vitro was significantly reduced during acute respiratory syncytial virus bronchiolitis but subsequently returned to normal. Nasopharyngeal and endotracheal interferon alfa were detected intermittently and in low concentrations. The degree of impairment of in vitro production and poor in vivo production of interferon alfa suggest the need for a therapeutic trial of nebulised or systemic interferon in acute bronchiolitis.

Infection by respiratory syncytial virus is one of the main causes of infant morbidity and mortality throughout the world causing annual winter epidemics of bronchiolitis with or without pneumonia, yet comparatively little is known about the mechanisms of resistance to—and recovery from—infection.[1] Maternal antibody does not completely protect against infection and some of the most severe infections occur in infants with the highest titres of passive antibody. Pre-existing secretory antibody in adults correlates with protection[2] but there is no good evidence of similar protection in infants,[3] although the appearance of secretory IgA correlates with falling titres of virus in infected infants.[4]

Local production of interferon is an important defence mechanism in many respiratory virus infections, and may limit viral replication until other host defence mechanisms (such as local and systemic antibody production) are activated. Little or no nasal interferon is produced in respiratory syncytial virus infection compared with other respiratory virus infections.[5 6] Nevertheless, respiratory syncytial virus is acutely sensitive to interferon in vitro[7] and evidence of poor interferon production suggests a disease in which the therapeutic use of interferon could be envisaged. The aim of the present study was to examine further the production of interferon in vitro and in vivo in infants with respiratory syncytial virus bronchiolitis.

Patients and methods

The index group comprised 64 infants aged 2 weeks to 12 months with a clinical diagnosis of bronchiolitis according to the criteria of Court,[8] with or without radiological evidence of pneumonia. All were confirmed as positive for respiratory syncytial virus by indirect immunofluorescence on nasopharyngeal secretions using a bovine antiserum against respiratory syncytial virus (Central Public Health Laboratory) and a fluorescein conjugated antibovine antiserum (Wellcome). Patients were classified by severity of disease into the following groups according to the amount of treatment they needed while in hospital: group I—oral feeds; group II—nasogastric feeds; group III—nasogastric feeds and supplemental oxygen; group IV—intravenous fluids and supplemental oxygen; and group V—artificial ventilation.

The index group were studied as soon as possible after admission to hospital (acute) and at least two weeks after clinical recovery (convalescent). The control group comprised age matched infants in hospital for non-infectious conditions, mainly cardiac or surgical patients.

Venous blood was obtained from the index group during the acute phase and during convalescence, and from the healthy controls, and heparinised. Peripheral blood mononuclear cells were obtained by separation on 'Ficoll-Paque' (Sigma), washed and resuspended at 1×10^6/ml in RPMI and 10% fetal calf serum, 60 μg/ml penicillin, 100 μg/ml streptomycin, and 300 μg/ml glutamine. Then 2×10^6 cells were incubated in 5% carbon dioxide with 50 haemagglutinating units of Newcastle disease virus (a potent in vitro stimulator of interferon alfa production) for 24 hours. A further 2×10^6 cells were incubated in 5% carbon dioxide for seven days in the presence of 50 μl phytohaemagglutinin (Wellcome) to stimulate production of interferon gamma. Supernatants were frozen at −70°C until assayed.

Nasopharyngeal secretions were obtained from index patients (serially when possible) during the acute phase of the infection by suction using a mucus aspirator and trap (Vygon) at the same time as routine nasal suction was being carried out. Endotracheal secretions were obtained from infants requiring artificial ventilation using the same mucus aspirator and a thin catheter.

Whenever possible serial tenfold dilutions of the nasopharyngeal or endotracheal secretions were made in phosphate buffered saline and 0·2 ml duplicate dilutions inoculated on to monolayers of HEp2 cells. These were grown in roller drums at 33°C for two weeks or until the typical cytopathic effect developed. The titre of respiratory syncytial virus in a specimen was taken as the reciprocal of the highest dilution in which the cytopathic effect was seen. Supernatants from the original secretions, diluted 5–10 times in phosphate buffered saline A, were frozen at −70°C until assayed for interferon.

In vitro mononuclear cell culture supernatants, and supernatants from nasopharyngeal and endotracheal secretions, were assayed for interferon alfa and interferon gamma with separate highly sensitive and specific immunoradiometric assays (Boots Celltech).

Statistical analysis was by Student's t test and χ^2 testing. Informed parental consent was obtained and the study was approved by the central Oxford research ethics committee.

Results

Peripheral blood mononuclear cell interferon alfa production in vitro was significantly lower in the 64 patients with acute respiratory syncytial virus infections than in the 21 control subjects (geometric mean (1 SD) 26·8 (6·5–109·6) compared with 138·9 (23·6–818·5) IU/ml, $p<0·001$) (fig 1). This was not caused by a primary defect in in vitro production of interferon alfa, because production of interferon alfa was normal in 22 of the patients with respiratory syncytial virus when they were convalescent (geometric mean (1 SD) 166·6 (55·6–500) IU/ml, $p<0·001$ compared with the patients with acute infections but not significantly different from the control subjects). There was no correlation between severity of disease and in vitro production of interferon alfa (fig 2).

There was no difference between in vitro production of interferon gamma by 41 patients during acute respiratory syncytial virus infection (geometric mean (1 SD) 39·3 (8·0–193·1) IU/ml), 14 convalescent patients (38·5 (8·3–179) IU/ml), and 20 control subjects (39·7 (5·7–277·3) IU/ml).

Interferon alfa was detected in 52 (45%) of 115 nasopharyngeal samples tested. It was generally present in small amounts (geometric mean titre (1 SD) 3·6 (1·1–11·3) IU/ml), although occasional high titres (one of 80 and one of 85 IU/ml) were recorded. Only single samples were available from 50 patients: 21 (42%) were positive with a geometric mean titre of 2·9 IU/ml. Multiple samples were available from 21 (more severely ill) patients, and of the 65 samples tested 31 (47·8%) contained interferon alfa at a geometric mean titre (1 SD) of 4·1 (1·4–11·8) IU/ml with a range of 1–20 IU/ml. Interferon alfa was intermittently detected in serial samples from a number of infants with severe bronchiolitis, and its presence or absence correlated poorly with the detection of the virus. Overall there

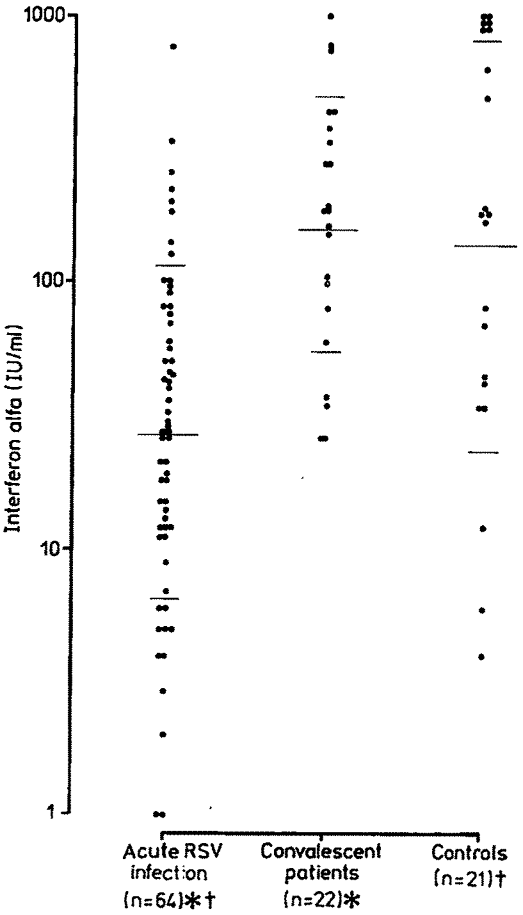


Fig 1 *In vitro interferon alfa production by peripheral blood mononuclear cells from 64 infants with acute respiratory syncytial virus (RSV) infection, 22 convalescent patients, and 21 control subjects. Wide bars=geometric mean, narrow bars=1 SD; *†p<0·001.*

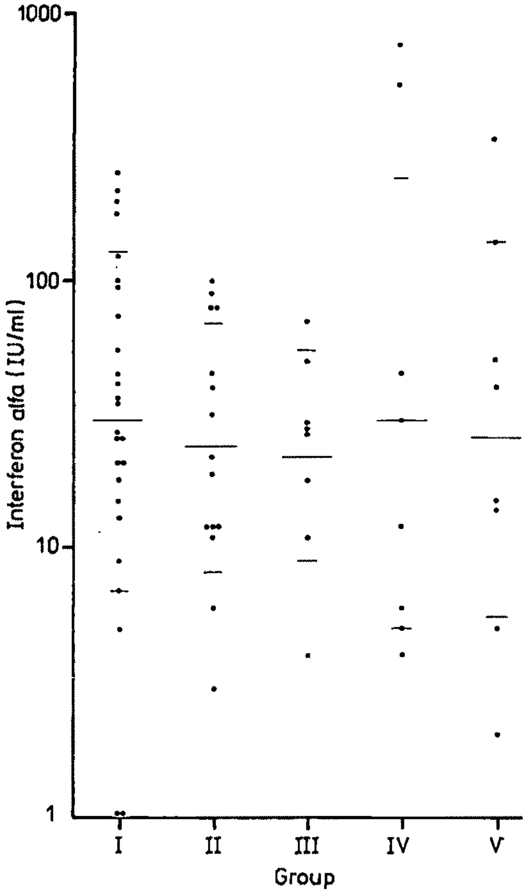


Fig 2 *In vitro interferon alfa production by peripheral blood mononuclear cells from infants with acute respiratory syncytial virus infection according to disease severity. Wide bars=geometric mean, narrow bars=1 SD. There was no significant differences among the groups.*

was no significant correlation between interferon alfa titres and titres of respiratory syncytial virus in nasopharyngeal secretions in which either interferon alfa or virus were detected (fig 3). In only one of the seven endotracheal aspirates tested was interferon alfa detected (titre 5 IU/ml). Interferon gamma was not detected in any of 16 nasopharyngeal and seven endotracheal samples tested.

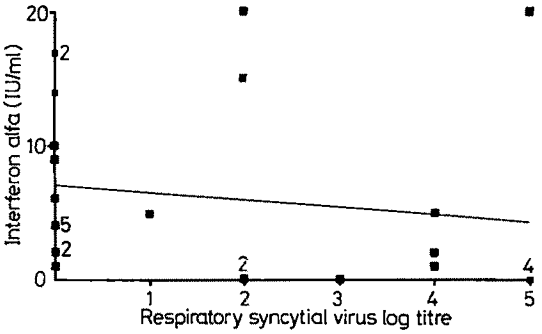


Fig 3 *In vitro interferon alfa titres and log respiratory syncytial virus titres on nasopharyngeal secretions from infants with acute respiratory syncytial virus bronchiolitis. Respiratory syncytial virus log titre is the reciprocal of greatest dilution that caused a cytopathic effect on HEp2 cells. Small numbers represent multiple superimposed values. y=7·0349–0·5507x, NS.*

Discussion

A number of features of respiratory syncytial virus infection are poorly understood. Mechanisms of resistance to and recovery from infection in infants are not clear, but neither serum antibody nor secretory antibody titres correlate well with protection or recovery. Cell mediated immunity (in the form of respiratory syncytial virus specific cytotoxic T cells) may be important in recovery and can sometimes be detected in the peripheral blood of even young infants.[9] There is a honeymoon period of six weeks after birth when infection and severe disease are unusual, but after this period almost all exposed infants become infected and about 40% develop lower respiratory tract infections.[10] Reinfections in childhood and into adult life, although successively milder, are common.[11] Up to 30% of infants with respiratory syncytial virus bronchiolitis later develop asthma, and the mechanism may be altered antigen presentation to the lungs after structural damage by respiratory syncytial virus. The new antiviral agent, ribavirin, has promising activity against respiratory syncytial virus but morbidity and mortality of severe respiratory syncytial virus infection remain high and it has not yet been shown whether ribavirin can reduce these.[12]

The results of this study, and those of Hall *et al*[5] and McIntosh,[6] suggest that it is unlikely that production of interferon alfa is an important in vivo mechanism for preventing or ameliorating respiratory syncytial virus infection. It is not understood why respiratory syncytial virus is such a poor inducer of interferon alfa, but this has now been shown both in vivo and in vitro.[13] We have also shown that there is significant but reversible impairment of the ability of mononuclear cells from infected infants to produce interferon alfa in vitro in response to a standard viral stimulus. Newcastle disease virus, a paramyxovirus, was deliberately chosen because it is similar to respiratory syncytial virus. Although the degree of impairment of production of interferon alfa could not be associated with the severity of the disease, it may well be an important sign of the transient suppressive effect of respiratory syncytial virus infection on interferon production.

Natural or recombinant interferon alfa has little or no therapeutic effect on respiratory virus infections when given intranasally or systemically after infection is established.[14] This is probably because respiratory viruses are generally potent stimulators of local, nasal, and sometimes serum production of interferon,[5 6] which may already be maximal by the time treatment with interferon can be started.

On the other hand, interferon alfa can be given prophylactically to prevent respiratory infections. Two recent studies have shown that an intranasal spray of interferon taken prophylactically by the family contacts of an index case with a cold, protected the contacts against developing colds caused by rhinoviruses, though not against infections due to parainfluenza, influenza, coronaviruses, or *Mycoplasma pneumoniae*.[15 16]

If the possible use of interferon against respiratory syncytial virus infection is to be considered there are two likely approaches: to use a nasal spray prophylactically in infants in contact with a cold (contact prophylaxis) or to use interferon to treat infants with established bronchiolitis (therapeutic use). Respiratory syncytial virus infections are generally introduced into the family by a schoolchild[11] so that it is theoretically possible to give an intranasal spray to parents to be given to a baby (perhaps any infants less than 6 months old or those at high risk of severe respiratory syncytial virus infection) when another family member develops a winter respiratory infection (contact prophylaxis). Current intranasal preparations have, however, caused considerable local toxicity in adults leading to nasal irritation, hyperaemia, bleeding, and ulceration[15 16] and it is likely that drops or sprays would be poorly tolerated by babies.

There is good reason to suspect that interferon might be successful in treating respiratory syncytial virus infection, even when infection is established. Local nasal production of interferon alfa is high during most respiratory virus infections but low during respiratory syncytial virus infection.[5 6] We have now shown that mononuclear cells from infants with respiratory syncytial virus bronchiolitis produce significantly less interferon alfa than cells from control subjects or cells from infants recovered from respiratory syncytial virus, suggesting a suppressive effect on production of interferon alfa by respiratory syncytial virus. On the other hand, respiratory syncytial virus is extremely sensitive to the action of interferon in vitro.[7] The combination of a virus that does not induce production of interferon but which is highly sensitive to its action—as in respiratory syncytial virus bronchiolitis—would seem ideal for a therapeutic trial of interferon. Because the main damage is occurring in the bronchioles nebulised interferon is likely to be the most effective form, and there is already evidence that nebulised interferon is well tolerated by adults.[17]

David Isaacs is funded by the Wellcome Trust and this work was also supported by a grant from the district research committee. I thank Trevor Berbick, Karen Sayer, and Elizabeth Vidale for technical help; Erica Woodward, her colleagues, and the nursing staff for help in collecting specimens; and Maggie Ellis for typing the manuscript.

References

1 McIntosh K, Fishaut MJ. Immunopathologic mechanisms in lower respiratory tract disease of infants due to respiratory syncytial virus. *Prog Med Virol* 1980;**26**:94–118.

2 Mills J, Van Kirk JE, Wright PF, *et al.* Experimental respiratory syncytial virus infection of adults. Possible mechanisms of resistance to infection and illness. *J Immunol* 1971;**107**:123–30.

3 Nandapalan N, Taylor C. Scott R, Toms GL. Mammary immunity in mothers of infants with respiratory syncytial virus infection. *J Med Virol* 1987;**22**:277–87.

4 McIntosh K, McQuillin J, Gardner PS. Cell-free and cell-bound antibody in nasal secretions from infants with respiratory syncytial virus infection. *Infect Immun* 1979;**23**:276–81.

5 Hall CB, Douglas RG Jr, Simons RL, Geiman JM. Interferon production in infants with respiratory syncytial, influenza and parainfluenza virus infections. *J Pediatr* 1978;**93**:28–32.

6 McIntosh K. Interferon in nasal secretions from infants with viral respiratory tract infections. *J Pediatr* 1978;**93**:33–6.

7 Moehring JM, Forsyth BR. The role of the interferon system in respiratory syncytial virus infections. *Proc Soc Exp Biol Med* 1971;**138**:1009–14.

8 Court SDM. The definition of acute respiratory diseases in children. *Postgrad Med J* 1973;**49**:771–6.

9 Isaacs D, Bangham CRM, McMichael AJ. Cell-mediated cytotoxic response to respiratory syncytial virus in infants with bronchiolitis. *Lancet* 1987;**ii**:769–71.

10 Hall CB. Respiratory syncytial virus. In: Feigin RD, Cherry JD, eds. *Textbook of pediatric infectious diseases.* 2nd ed. Philadelphia: Saunders, 1987:1653–76.

11 Hall CB, Geiman JM, Biggar R, *et al.* Respiratory syncytial virus infections within families. *N Engl J Med* 1976;**294**:414–9.

12 Isaacs D. Ribavirin. *Pediatrics* 1987;**79**:289–91.

13 Chonmaitree T, Roberts NJ, Douglas RG, Hall CB, Simons RL. Interferon production by human mononuclear leukocytes: differences between respiratory syncytial virus and influenza viruses. *Infect Immun* 1981;**32**:300–3.

14 Scott GM, Tyrrell DAJ. Interferon: therapeutic fact or fiction for the '80s? *Br Med J* 1980;**280**:1558–62.

15 Douglas RM, Moore BW, Miles HB, *et al.* Prophylactic efficacy of intranasal alpha$_2$-interferon against rhinovirus infections in the family setting. *N Engl J Med* 1986;**314**:65–70.

16 Hayden FG, Albrecht JK, Kaiser DL, Gwaltney JM. Prevention of natural colds by contact prophylaxis with intranasal alpha$_2$ interferon. *N Engl J Med* 1986;**314**:71–5.

17 Greenberg SB, Harmon MW, Cough RB, *et al.* Prophylactic effect of low doses of leukocyte interferon against infection with rhinovirus. *J Infect Dis* 1982;**145**:542–6.

Correspondence to Dr D Isaacs, Infectious Disease Unit, Department of Paediatrics, John Radcliffe Hospital, Oxford OX3 9DU.

Accepted 8 August 1988

Archives of Disease in Childhood, 1989, **64,** 96–102

Growth and other factors affecting peak expiratory flow rate

J W K CARSON,* H HOEY,*† AND M F H TAYLOR*†

**National Children's Hospital and †Department of Paediatrics, Trinity College, Dublin*

SUMMARY By means of a simple questionnaire and measurements of height, weight, and peak expiratory flow rates 3061 children from city and rural populations were studied. Children with asthma or other respiratory diseases had lower peak expiratory flow rates, and younger children living in rural areas had higher rates. In 2828 healthy children the peak expiratory flow rate increased with age, height, and weight. There was an increase in the slope of this line for both age and height—at 12 years and 145 cm in girls, and at 14 years and 155 cm in boys. This continued for two to three years and 15 cm, respectively, before it declined. Previous surveys have obscured this change associated with height by reporting small numbers and using linear regression analysis. This type of analysis can underestimate the mean peak expiratory flow rate of small children by half to one standard deviation. A centile graph against age is recommended to describe normal values and their differences.

The Wright peak flow meter[1] is a practical and common way of measuring peak expiratory flow rate. It is easy to use, even for 3 to 5 year old children.[2] Lunn measured peak expiratory flow rate (PEFR) in over 3000 children,[3] but his study was limited to city children aged 6 to 11 years; unhealthy children were not excluded and local air pollution was high.[4] Other studies in normal children have been small and largely confined to city populations.[5–9] We report the results of a study comprising over 3000 children aged 4 to 18 years drawn from both city and rural populations.

Subjects and methods

Children at school in the city of Dublin (population about 800 000), and smaller centres (population 5000–15 000) within 60 miles of Dublin, were surveyed with their parents' consent. A questionnaire was distributed to the parents enquiring about chronic illnesses (table 1). Height was assessed with a portable stadiometer by the same investigator throughout the study. Weight in underclothes was measured with an electronic balance. PEFR was measured with a Wright flow meter. Four meters were used and were calibrated by one of the authors against the manufacturer's submaster meter which is used to calibrate all new meters before issue. After the method had been shown to a group of five children, each child had two or three practice blows, before three test blows done standing up with the neck held vertically and the tube of the meter held horizontally. The highest value reached was taken as the PEFR for that child. Social class was assessed according to the Registrar General's classification.[10]

Results

A total of 3061 children, 1528 boys and 1533 girls aged 4–19 years, were included in the analysis. Heights were not available for 79 children due to a fault in the stadiometer, and 233 children were excluded from the analysis of healthy children because of a chronic illness (assessed by the questionnaire), or an upper respiratory tract infection at the

Table 1 *Questionnaire completed by parents*

Does your child have:	Please tick:	
	Yes	No
1 Asthma	( )	( )
2 Chronic chest infection	( )	( )
3 Coeliac disease (on gluten free diet)	( )	( )
4 Chronic kidney disease	( )	( )
5 Other long term illness requiring regular hospital attendance:	( )	( )

Please name illness ....

time of study. Eighty seven boys and 49 girls had asthma (4·4% of the total) (table 2), and 63 (35 boys and 28 girls) had no asthma but either chronic chest infections, atopic symptoms, or an upper respiratory tract infection at the time of the study; 34 (11 boys and 23 girls) had other non-respiratory chronic illnesses. There was no predisposition to ill health in any social class. Asthma was commoner in the 1550 city children (5·1%) than in the 1511 rural children (3·8%) but this difference was not significant.

Children with asthma had a mean PEFR 18·4 l/minute lower than the healthy children (p<0·001). Those with other respiratory diseases had a mean PEFR 37·3 l/minute lower than the healthy children (p<0·001). Overall, rural children had a significantly higher mean PEFR (+3·8 l/minute) than those living in the city (p=0·032). Similar analysis for children under 12 years, however, showed a greater difference (mean+15·0 l/minute for rural children), but in those over 12 years old rural children had a lower PEFR (mean −8·0 l/minute) than those living in the city.

Table 2 *Distribution by age and height of 135 asthmatic and 2847 non-asthmatic children*

	Asthmatic	*Non-asthmatic*
Age (years):		
4–5	0	20
5–6	3	193
6–7	7	194
7–8	7	218
8–9	18	237
9–10	13	194
10–11	10	181
11–12	15	223
12–13	8	168
13–14	11	216
14–15	12	227
15–16	7	199
16–17	7	196
17–18	7	207
18–19	10	174
Height (cm):		
90–95	0	1
95–100	0	3
100–105	0	42
105–110	3	86
110–115	2	151
115–120	6	173
120–125	10	206
125–130	10	215
130–135	19	214
135–140	8	183
140–145	11	149
145–150	13	147
150–155	15	192
155–160	5	244
160–165	4	254
165–170	15	219
170–175	3	164
175–180	7	127
>180	4	77

Values are greater than lower limits and less than or equal to upper limits for each group.

Multilinear regression analysis of PEFR against the following independent variables was done: height, age and weight, rural dwelling, social class, asthma, other respiratory disease, and other non-respiratory chronic disease (table 3). PEFR was not significantly associated with social class (whether taken as individual social classes or divided into two groups, manual and non-manual) or to non-respiratory chronic disease. Height, weight, age, and sex had a significant effect on PEFR (p<0·001). Linear regression analysis on the groups studied are shown in table 4.

There were 2828 healthy children, 1395 boys and 1433 girls, and the distribution of children by age is shown in table 5. The values for mean, standard deviation, and centiles of PEFR in age, height and weight groups are shown in tables 5, 6, and 7. Among girls there was a significant increase in the slope of the PEFR/age line at 12 years, which continued for two years (fig 1). A similar increase was seen in the slope of the PEFR/height line starting at 145 cm and continuing for 15 cm (fig 2). In both cases the change in slope was significant (p<0·0001). There was little increase in PEFR after this among girls. Among boys this change occurred at 14 years and at 155 cm, and continued for similar periods (fig 1 and 2). There was continued increase in PEFR among boys up to 19 years of age.

When the healthy rural children were compared with city children of the same height (table 8) the boys had higher PEFRs up to a height of 145 cm, and the girls from rural areas had higher PEFRs up to a height of 165 cm. In the group from the rural areas, the smaller girls had similar or higher PEFRs to the boys up to a height of 165 cm. When a similar comparison was made grouping the children by age

Table 3 *Multilinear regression analysis of 2982 children with accurate details on all variables*

Variable	*Regression coefficient*	*p Value (two tailed)*
Intercept	−143·8	<0·001
Height	+1·91	<0·001
Weight	+2·24	<0·001
Age	+11·01	<0·001
Male sex	+20·6	<0·001
Asthma	−18·4	<0·001
Other respiratory disease	−37·3	<0·001
From rural area	+3·81	0·032

Table 4 *Linear regression analysis of PEFR against height*

	a	*b*	*No of children*	*Correlation coefficient*	*Standard error of the estimate*
			*Healthy**		
All					
Boys	5·5985	−439·78	1395	0·9151	56·75
Girls	5·1903	−390·58	1357	0·9053	47·24
Country					
Boys	5·2416	−388·85	706	0·9086	55·68
Girls	4·9363	−343·42	641	0·9072	44·83
City					
Boys	5·9674	−493·88	689	0·9230	56·65
Girls	5·5611	−454·38	716	0·9165	46·11
			*Healthy and unhealthy**		
City					
Boys	5·9419	−492·55	771	0·9193	57·67
Girls	5·5551	−454·48	779	0·9145	46·74
			Healthy boys and girls together†		
City	91·3	65·858	1405	0·9213	52·32
			All healthy‡		
Boys	0·006760	1·5585	1395	0·9213	0·06564
Girls	0·007225	1·4883	1357	0·8985	0·06845

*PEFR=a×(height in cm)+b; †PEFR=a×(height in metres)^3+b; ‡log PEFR=a×height+b.

Table 5 *Peak expiratory flow rates by age in centiles for 2828 healthy children*

Age (years)	*Sex*	*No of children*	*Mean (SD) peak expiratory flow rate for each group*	*Peak expiratory flow rate at:* *97th centile*	*90th centile*	*50th centile*	*10th centile*	*3rd centile*
4–5	M	8	207 (58)	290	290	180	125	125
	F	12	162 (52)	280	215	155	110	105
5–6	M	91	195 (41)	275	250	195	140	130
	F	88	180 (35)	260	225	180	135	125
6–7	M	97	217 (39)	290	270	215	165	145
	F	91	198 (38)	270	250	195	150	115
7–8	M	102	242 (43)	320	305	240	190	170
	F	109	231 (37)	295	280	230	185	155
8–9	M	112	276 (45)	350	330	280	210	195
	F	119	258 (39)	350	320	250	215	200
9–10	M	90	306 (49)	390	375	300	245	205
	F	98	290 (39)	345	340	285	235	215
10–11	M	79	325 (45)	405	380	335	250	235
	F	95	305 (42)	375	355	300	245	235
11–12	M	100	353 (48)	425	405	355	290	245
	F	115	333 (47)	410	385	335	265	250
12–13	M	88	377 (47)	485	430	375	310	300
	F	103	369 (49)	450	435	370	305	275
13–14	M	116	404 (60)	525	495	405	330	300
	F	109	421 (48)	505	490	425	355	340
14–15	M	100	450 (64)	570	535	445	365	335
	F	135	440 (46)	520	500	440	385	355
15–16	M	107	499 (72)	615	595	505	400	340
	F	93	448 (51)	545	510	450	385	350
16–17	M	101	552 (63)	650	620	565	475	400
	F	97	460 (45)	550	525	455	400	390
17–18	M	109	569 (66)	695	640	570	480	430
	F	94	468 (49)	550	525	475	405	370
18–19	M	95	602 (64)	720	690	605	515	485
	F	75	478 (47)	555	535	485	420	380

Figures given as unsmoothed values. Values are greater than lower limit and less than or equal to upper limit for each group.

Table 6 *Peak expiratory flow rates by height for 2752 healthy children. Figures are shown for boys/girls*

Height (cm)	*No of children*	*Mean (SD) peak expiratory flow rate for each group*	*Mean peak expiratory flow rate at:*		
			90th centile	*50th centile*	*10th centile*
90–95	1/0	131/0 (0/0)	0/0	0/0	0/0
95–100	1/2	170/188 (0/54)	0/0	0/0	0/0
100–105	18/22	168/161 (30/35)	210/190	165/175	125/115
105–110	41/41	193/174 (37/44)	240/215	190/170	145/125
110–115	65/79	206/194 (40/37)	255/240	205/195	160/155
115–120	79/86	222/214 (44/46)	260/260	210/210	185/160
120–125	95/106	250/244 (42/41)	305/290	250/240	195/195
125–130	90/116	269/273 (43/43)	320/335	270/270	210/220
130–135	96/112	297/299 (49/51)	355/360	305/290	240/235
135–140	80/94	326/308 (41/44)	385/360	330/305	265/250
140–145	77/67	344/332 (41/52)	390/395	350/335	280/265
145–150	87/57	365/370 (38/52)	415/440	365/370	310/305
150–155	89/98	382/409 (53/48)	455/475	380/410	315/345
155–160	71/167	412/443 (54/46)	485/510	415/445	345/385
160–165	75/171	469/457 (72/51)	575/520	460/460	395/390
165–170	111/99	514/470 (77/48)	605/525	515/470	420/405
170–175	129/30	545/484 (69/47)	635/525	545/490	455/420
175–180	118/8	568/493 (69/53)	660/0	570/0	485/0
>180	72/2	584/474 (69/6)	675/0	585/0	510/0

Figures given as unsmoothed values.

Table 7 *Peak expiratory flow rates, by weight for 2828 healthy children. Figures are shown for boys/girls*

Weight (kg)	*No of children*	*Mean (SD) peak expiratory flow rate for each group*	*Mean peak expiratory flow rate at:*		
			90th centile	*50th centile*	*10th centile*
<15	2/2	179/163 (67/19)	0/0	0/0	0/0
15–20	103/108	191/185 (38/47)	250/235	190/180	145/130
20–25	197/221	237/225 (43/47)	290/280	235/225	180/165
25–30	183/202	287/274 (52/46)	355/335	290/270	220/215
30–35	143/135	328/318 (50/50)	390/385	335/310	255/255
35–40	121/113	370/347 (48/49)	430/400	365/355	310/275
40–45	98/113	391/400 (51/53)	455/470	385/400	335/330
45–50	80/148	430/431 (69/53)	515/505	430/430	340/365
50–55	97/159	480/449 (70/48)	575/510	485/445	400/390
55–60	106/114	526/465 (70/52)	605/525	535/470	425/405
60–65	107/70	551/471 (72/48)	630/520	560/475	445/410
65–70	78/31	592/471 (63/38)	685/510	590/470	520/425
70–75	46/13	589/486 (65/52)	680/0	585/0	505/0
75–80	18/3	553/480 (73/47)	645/0	540/0	440/0
80–85	9/0	610/0 (71/0)	0/0	0/0	0/0
>85	7/1	610/464 (71/0)	0/0	0/0	0/0

Figures given as unsmoothed values.

instead of height, however, there was little difference between the rural and city children.

Discussion

Our results confirm that children with respiratory disease have lower values of PEFR than normal children. Those children with respiratory disease but no history of asthma had a particularly low mean PEFR, which suggests that some of these children had asthma and were not getting appropriate treatment.[11]

Although our study showed a significantly higher mean PEFR in the rural children, this difference was greater among the children under 12 years. The inclusion of older rural children as boarders in the city secondary schools may have increased the level of PEFR in these older age groups, but we have no

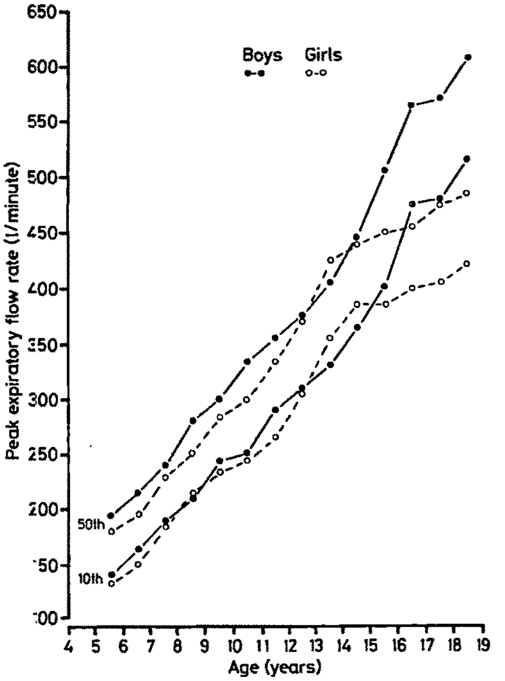


Fig 1 *Peak expiratory flow rate and age, 10th and 50th centile lines (unsmoothed values).*

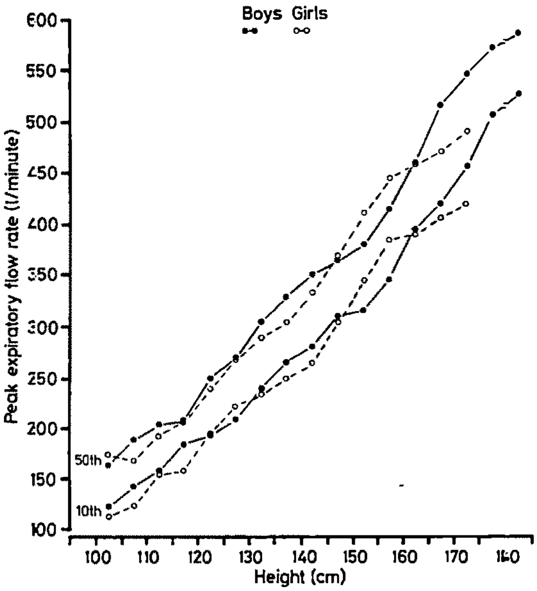


Fig 2 *Peak expiratory flow rate and height, 10th and 50th centile lines (unsmoothed values).*

record of the numbers of rural boarders in city schools. Air pollution may have been another factor.

The median smoke levels in Dublin at the time of the study were between 25–80 μg/m^3.[12] In Sheffield (where Lunn's study was carried out) the mean daily figures in the winter 1965–6 were 97–301 μg/m^3.[4] The lower air pollution and the inclusion or rural children boarding in city schools in the present study may account for the higher PEFR values in the city children when compared with the results from Sheffield and with the other studies of city children in the 1960s (table 9). In addition the Sheffield study did not exclude unhealthy children.

When the results of the study by Godfrey *et al*[7] are compared with our results for city children analysed in the same way (linear regression) the results are similar in the younger children (table 9). There is good correlation for the girls throughout, and for boys below 135 cm in height. Above this, the difference increased from 21 to 45 l/minute. Not all the differences can be satisfactorily explained. Factors such as smoking by the children or their parents were not assessed in either study. Genetic differences as shown by measurement of lung volumes of children of different races[13] may also be a factor.

In this study the centile method of analysis gives a much higher mean value for PEFR in small and tall children than linear regression. Linear regression might give a poor estimate of central tendency at the extremes of the data and would also conceal the peripubertal acceleration. The linear regression method underestimates the PEFR in small children by 30 l/minute for boys and 19 l/minute for girls. These differences are close to one standard deviation for boys and half a standard deviation for girls. There are similar but smaller differences among taller children, where the regression analysis underestimates the value for boys and overestimates the value for girls (table 9). Smoothing for centile lines also has the disadvantage of concealing the peripubertal acceleration.

In other smaller studies the results have been presented as a linear correlation with height[5–8] or as an exponential of height.[8 9] The PEFR/height graphs of Nairn *et al*[5] showed a similar pattern to our results, but they used a linear regression analysis relating PEFR to height as have many studies of forced expiratory volume in one second,[5–7] which have shown a similar pattern in their graphs.[14 15]

This is the largest study of PEFR in healthy children so far reported. The results show that changes take place in PEFR about the time of puberty but are not in phase with other growth changes. These changes have been obscured in

Table 8 *Mean peak expiratory flow rates of 2752 healthy children by height and where they lived. Figures are shown for boys/girls*

Height (cm)	*Children living in city (n=1409)*		*Children living in rural areas (n=1343)*		*Difference between mean peak expiratory flow rate in rural and city children*
	No of children	*Mean peak expiratory flow rate*	*No of children*	*Mean peak expiratory flow rate*	
90–95	1/0	131/0	0/0	0/0	0/0
95–100	1/2	170/188	0/0	0/0	0/0
100–105	5/8	155/135	13/14	173/175	18/40
105–110	18/18	173/159	23/23	208/186	35/27
110–115	30/40	197/180	35/39	213/209	−2/41
115–120	39/41	223/192	40/45	221/233	22/34
120–125	37/50	236/226	58/56	258/260	11/29
125–130	42/47	263/256	48/69	274/285	11/29
130–135	45/50	289/276	51/62	305/316	16/40
135–140	38/48	323/292	42/46	328/325	5/33
140–145	41/44	342/322	36/23	346/350	4/28
145–150	42/33	365/357	45/24	365/387	0/30
150–155	43/64	386/405	46/34	378/417	−8/12
155–160	35/98	421/438	36/69	404/449	−17/11
160–165	46/89	475/454	29/82	460/459	−15/5
165–170	55/64	517/470	56/35	511/470	−6/0
170–175	63/17	555/482	66/13	535/487	−20/−5
175–180	64/3	581/485	54/5	553/498	−28/13
>180	46/2	593/474	26/0	568/0	−25/0

Table 9 *Expected values of PEFR for given height according to different sources and methods of analysis (boys/girls)*

	Total No	*Height (cm)*				
		105	*115*	*135*	*155*	*170*
This study						
All healthy						
Centile chart	2752	178/173	208/203	318/298	400/428	530/480
Linear regression	2752	148/154	204/206	316/310	428/414	512/492
Healthy in rural areas*	1347	162/175	214/224	319/323	424/422	502/496
Healthy in cities*						
This study	1405	133/130	192/185	312/296	431/408	521/491
Godfrey *et al*[7]	382	132/132	185/185	291/290	397/396	476/475
Murray and Cook[8]	220	120/144	178/191	290/284	404/377	490/447
Weng and Levison[6] (boys and girls combined)	139	139	185	283	381	454
Healthy and unhealthy in cities*						
This study	1347	131/128	191/184	310/295	428/407	518/490
Lunn[3]	3556	—	175/167	254/251	—	—
Healthy in cities† (boys/girls combined)						
This study	1405	172	205	290	406	514
Bjure *et al*[9]	214	—	206	274	365	451

*Linear regression; †linear regression based on height in m^3.

previous studies by the types of analysis used. The timing of the increase in the slope of the PEFR against age, height, or weight lines may depend on the timing of puberty, and this varies in different countries. The mean (SD) age of menarche for Irish girls is 13·5 (1·3) years.[16] In the girls in this study the spurt in PEFR overlaps the menarche, and so follows the height spurt that normally precedes the menarche.

In view of these findings we suggest that a 'centile chart' approach to normal values of PEFR is a more appropriate representation of normal values than the conventional straight line graph usually used for children. A centile chart is the accepted method of presenting normal values for height and weight, and it seems sensible to apply it to pulmonary function as well. Charts of PEFR for age (figs 3 and 4 based on table 5) rather than height are probably more

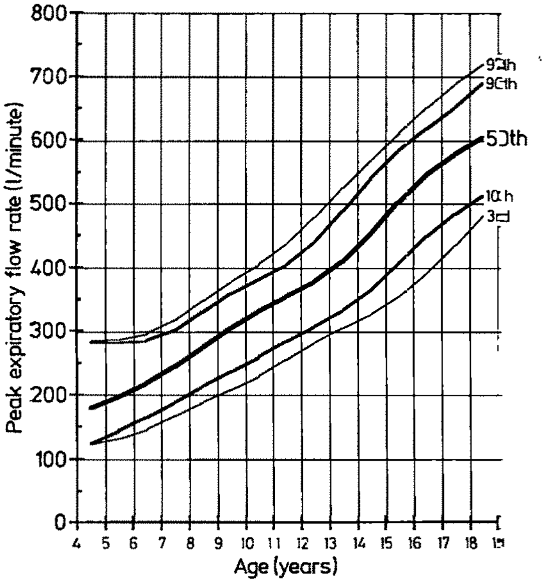


Fig 3 *Peak expiratory flow rate and age; centile chart for boys (smoothed values).*

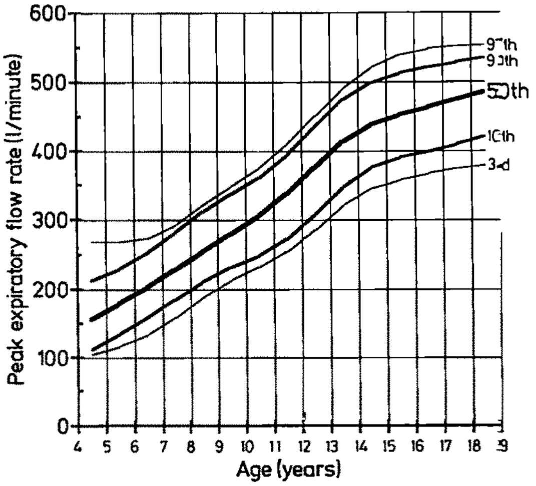


Fig 4 *Peak expiratory flow rate and age; centile chart for girls (smoothed values).*

convenient for rapid reference in an accident and emergency department or a busy general practice when accurate heights are not readily available.

We thank the children, their parents, and their teachers whose cooperation was essential for the completion of this study, as well as our many helpers in the National Children's Hospital and Trinity College, Dublin.

References

[1] Wright BM, McKerrow CB. Maximum forced expiratory flow rate as a measure of ventilatory capacity. *Br Med J* 1959;**ii:** 1041–7.

[2] Milner AD, Ingram D. Peak expiratory flow rates in children under 5 years of age. *Arch Dis Child* 1970;**45:**780–2.

[3] Lunn JE. Respiratory measurements of 3,556 Sheffield schoolchildren. *British Journal of Preventive and Social Medicine* 1965;**19:**115–22.

[4] Lunn JE, Knowelden J, Handyside AJ. Patterns of respiratory illness in Sheffield infant schoolchildren. *British Journal of Preventive and Social Medicine* 1967;**21:**7–16.

[5] Nairn JR, Bennett AJ, Andrew JD, MacArthur P. A study of respiratory function in normal school children. *Arch Dis Child* 1962;**36:**253–8.

[6] Weng T-R, Levison H. Standards of pulmonary function in children. *Am Rev Respir Dis* 1969;**99:**879–94.

[7] Godfrey S, Kamburoff PL, Nairn JR. Spirometry, lung volumes and airway resistance in normal children aged 5 to 18 years. *Br J Dis Chest* 1970;**64:**15–24.

[8] Murray AB, Cook CD. Measurement of peak expiratory flow rates in 220 normal children from 4·5 to 18·5 years of age. *J Pediatr* 1963;**62:**186–9.

[9] Bjure J, Dalen G, Kjellman B. Peak expiratory flow rate. Reference values for Swedish children. *Acta Paediatr Scand* 1979;**68:**605–7.

[10] Registrar General. *Classification of occupations 1970.* London: HMSO, 1971.

[11] Speight ANP, Lee DA, Hey EN. Underdiagnosis and undertreatment of asthma in childhood. *Br Med J* 1983;**286:**1253–6.

[12] Riley P. *Environment pollution report 1983/4.* Dublin: Health inspectorate, atmospheric pollution and noise control unit, Dublin Corporation, 1984.

[13] Binder RE, Mitchell CA, Schoenberg JB, Bouhuys A. Lung function among black and white children. *Am Rev Respir Dis* 1976;**114:**955–9.

[14] Strang LB. The ventilatory capacity of normal children. *Thorax* 1959;**14:**305–10.

[15] Dickman ML, Schmidt CD, Gardner RM. Spirometric standards for normal children and adolescents (ages 5 years through 18 years). *Am Rev Respir Dis* 1971;**104:**680–7.

[16] Hoey H, Cox L, Tanner J. The age of menarche in Irish girls. *Ir Med J* 1986;**79:**283–5.

Correspondence to Dr JWK Carson, National Children's Hospital, Harcourt Street, Dublin 2, Ireland.

Accepted 14 June 1988

Archives of Disease in Childhood, 1989, **64,** 103–107

School holidays and admissions with asthma

J STORR AND W LENNEY

Royal Alexandra Hospital for Sick Children, Brighton

SUMMARY The admission rate for asthma at a children's hospital was studied over an 11 year period. Admissions varied unpredictably over periods of a few days, but there was a repeated yearly pattern of peaks and troughs with an interval of several weeks. The short term variation could be attributed to chance effects alone, excluding any important role for short term influences—for example, weather changes—in precipitating asthma admissions. There was a definite association between the longer term variation and school holidays. The admission rate fell during holidays and there were two or more peaks during terms. The pattern is consistent with a largely viral aetiology for asthmatic attacks throughout the year. We postulate that school holidays disrupt the spread of viral infections in a community, with synchronisation of subsequent attacks. Travel during holidays may facilitate acquisition of new viral strains by the community.

The number of admissions of children with asthma is seasonal,[1 2] with a large peak in autumn and a smaller peak in spring; the spring rise coincides with the hay fever season.[3 4] Before the autumn rise is an August fall,[1] which suggests a possible link with the school summer holidays. The sharp rise in September occurs after mould spore and pollen counts have plateaued,[5] but before the main winter rise in respiratory tract infections. This is probably a combined mechanism of viral infection and increased bronchial hyper-reactivity due to exposure to airborne allergens during the summer months.[6 7]

Admissions with asthma also vary considerably over periods of a few days. Epidemic days are associated with low temperature and humidity,[8] with thunderstorms or sudden rain,[9–11] and with sudden falls in temperature.[12 13] Many parents have reported associations with changes in the weather.

The aims of this study were to determine the significance, if any, of variation in asthma admissions over periods of a few days, and to look for an association between seasonal trends and timing of school holidays.

Material and methods

Date of birth, dates of admission and discharge, sex, and area code were obtained for all admissions to this hospital for the years 1975–1985. The data were obtained from the Hospital Activity Analysis using the International Classification of Diseases code 493. The data were transferred to a microcomputer and checked for accuracy against surviving hospital records. Dates of past school holidays were obtained from the local department of education, and the dates adjusted to include any adjacent weekends. The autumn half term break was treated as a holiday, but the shorter half term breaks were ignored.

To examine seasonal trends, the rate of admissions with asthma was plotted daily as a five day moving average. The association with school holidays was also examined year by year. A pattern linking admissions with asthma to school holidays was first determined by inspection, then subjected to statistical analysis. The combined data for the 11 years are shown in figs 1 and 2: the mean starting dates of holidays and terms are indicated by dotted lines, and the admissions are plotted at their correct relative position within each term or holiday period. The figures therefore show the mean daily admission rate, with the dates of all terms and holidays precisely superimposed.

To examine short term variation in the rate of admissions with asthma, the 11 year period was divided into three day segments starting on 1st January 1975. A prediction for the number of periods within which 0, 1, 2, 3, . . . asthma admissions had occurred was determined from the Poisson distribution. This was calculated separately for each month of the year to exclude any influence of longer term trends. In a similar analysis, data were stratified by area of residence into three broad groups: coast, downs, and other. This was to look for local

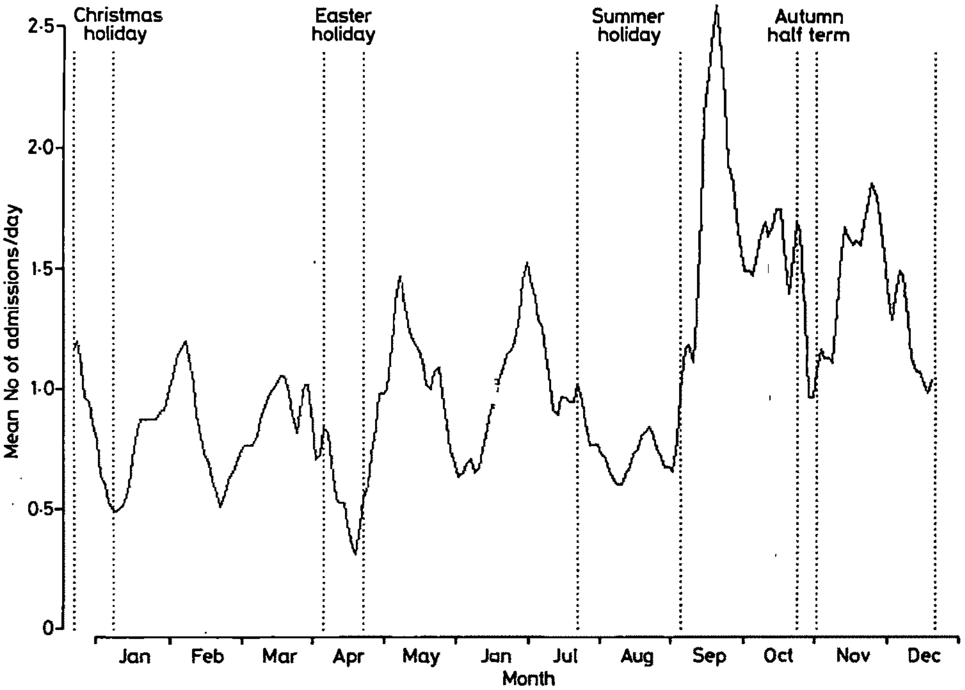


Fig 1 *Cumulative yearly trends (1975–85) in asthma admission rate: all children, 0–16 years.*

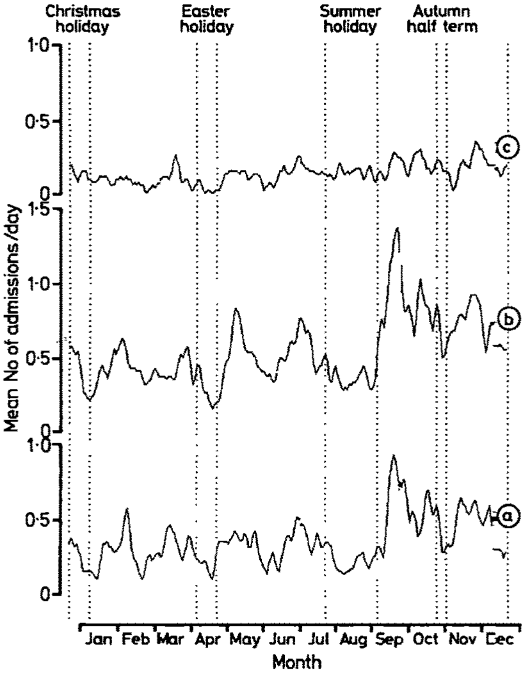


Fig 2 *Cumulative yearly trends 1975–85 in asthma admission rate: (a) 0–3 years, (b) 4–10 years, and (c) 11–16 years.*

influences that might operate in the short term such as the release of fungal spores by a sea mist, or the storm of airborne allergens created by ploughing or harvesting.

The significance of the difference between actual and predicted clustering was determined by the χ^2 test. To avoid random inflation of significance, an appropriately smaller critical p value was used for analyses by area. As there were three areas, the value chosen was one third of p=0·05—that is, p=0·017. Differences in rates of admission within holiday periods were assessed by the Wilcoxon signed rank test, and the suitability of a 'two peak/term' model was tested by least squares regression for longitudinal data, and by the χ^2 test for summated data.

Results

The seasonal pattern of admissions with asthma is shown in fig 1 and fig 2. There was a repeated yearly pattern that was not lost by summing the data for the 11 years. Fig 1 shows the pattern for all children, and fig 2 shows that for children in the age groups: 0–3 years (preschool), 4–10 years (primary school), and 11–16 years (secondary school). Older children contributed little to the overall pattern primarily because admissions were fewer, but the pattern is similar though less pronounced. The two younger age groups showed patterns that were remarkably similar both in shape and timing.

The pattern was of a falling admission rate during holidays ($p<0{\cdot}005$) followed by two major peaks in each term ($p<<0{\cdot}0001$ in each case). One or two smaller peaks commonly occurred in the autumn term. The largest peak always occurred after the summer holiday.

The distribution of clusters of admissions in three day periods is shown in the table. The distributions were not significantly different from those predicted by the Poisson distribution. Any recurring climatic or other factor operating in the short term should have produced a significant effect, even if only 5–10% of all admissions were precipitated by it. The trend towards significance was greatest in coastal areas ($p=0{\cdot}04$, critical value of $p=0{\cdot}017$).

Discussion

The number of admissions of children with asthma in Brighton over an 11 year period showed a repeating pattern of a decrease during school holidays and at least two major peaks during the subsequent terms. The largest peak occurred after the longest holiday. Troughs between peaks during term time corresponded roughly with half term breaks.

The most likely reason for the pattern is that most attacks of asthma in children that require admission to hospital are associated with viral respiratory tract infections. These infections do not seem to be limited to the winter months, and school holidays reduce the opportunity for the spread of viral infections in a community, which may have the effect of synchronising subsequent attacks. Holiday travel may result in the acquisition of new viral strains by the community.

Alternative explanations of the association seem less plausible. The fall in the admission rate during the summer holidays may reflect travel away from Brighton, but as a holiday resort this should be countered by a larger influx, and national data show identical falls.[2 3] One of the commonest allergens, the house dust mite, is more likely to be encountered in the home than at school, and an allergic factor should also exert a greater effect on older children, a larger proportion of whom are atopic.[14] Stress is an important precipitator of asthmatic attacks, but it is not clear why the stress of returning to school should cause attacks one or two weeks later, or why admission rates do not drop sharply on the first day of each holiday. It is equally difficult to

Table *Comparison of clustering in three day periods of asthma admissions, 1975 to 1985, with clustering predicted by the Poisson distribution*

No in three day period	*No of actual and predicted occasions on which a group of particular size occurred*							
	Total		*Coast*		*Downs*		*Other*	
	Actual	*Predicted*	*Actual*	*Predicted*	*Actual*	*Predicted*	*Actual*	*Predicted*
0	186	161	344	321	606	576	1086	1084
1	272	257	392	372	400	426	216	221
2	258	256	259	276	189	206	33	30
3	200	209	141	172	91	84	2	3
4	136	155	82	97	33	31	1	0
5	82	108	60	52	8	10		
6	60	73	22	26	7	3		
7	40	47	12	13	2	1		
8	44	30	9	6	2	0		
9	18	19	12	2				
10	14	11	2	1				
11	6	6	1	0				
12	7	4	1	0				
13	5	2	0	0				
14	5	1	1	0				
15	2	0						
16	2	0						
17	0	0						
18	1	0						
χ^2 (df)	20·9 (13)		17·5 (9)		6·14 (6)		0·19 (2)	
p Value	0·075		0·04		0·4		0·9	
Critical p value	0·05		0·017		0·017		0·017	

see how stress could affect children too young to go to school. A further possibility could be that drugs are taken more regularly during school holidays. Again, this seems an unlikely explanation in preschool children, most of whom are unable to use effective prophylactic drugs. Viral infections, however, are readily transmitted between children during term time, and to preschool children by their elder siblings.

Many studies have shown that viral infection is an important precipitator of asthma in childhood. A community study[15] found that wheezing was a common symptom, predominantly associated with signs of viral upper respiratory tract infection, and with a seasonal pattern identical to that of viral infection in children who did not wheeze. Wheezing is most common in preschool children, but there is an increased incidence at the age of starting school.[16] Viruses have been isolated from 42% of children aged 1–5 with wheezing attacks.[17] Viral infections are not limited to the winter months,[18] and children may be remarkably well between attacks.[17] In some children the wheezing may be a result of sensitisation to the virus by an earlier infection.[19] It is possible that many infections that initiate an attack of wheezing are aborted early and therefore not readily detected.

Our study does not provide evidence that wheezing is a short term response to environmental factors; the only suggestion of abnormal clustering was among children from the coastal region (table). Although this did not reach the set level of significance, it is likely to have been a real effect. As most of the excessive clustering occurred at times of expected high incidence, rapid spread of viral infections in the larger coastal communities remains the most likely explanation.

Any pronounced effect of variables such as changes in the weather should have been readily detectable. Our results are compatible with the findings of Khan, however, who showed that such factors seem to play only a minor part in the aetiology of attacks (5–15% of total variance).[20] More recently, Carey and Cordon suggested that clusters of admissions for asthma are associated with wind direction.[21] Their statistical analysis was comparatively unsophisticated, however, and the association that they reported is meaningless because any two factors that undergo seasonal variation must have a statistical relationship. The potential importance of temporal variation to asthma research is a point worth emphasising.

Most studies of airborne allergens have shown a poor correlation with asthma attacks.[12 20 22–24] Matters have been complicated by the finding that aerosols laden with allergens, with greater ability to penetrate small airways, may only be produced in particular weather conditions, particularly during periods of rainfall.[25] Gross environmental pollution with organic dusts may cause sudden increases in admissions for asthma.[26–28] It seems likely, however, that variations in concentrations of allergens in the atmosphere do not usually produce sufficient day to day variation in asthma to precipitate hospital admissions.

Allergens, particularly the house dust mite, are of considerable importance in asthma. Exposure to allergens produces chronic inflammation of the airways and an increase in bronchial hyperirritability.[29] Not all asthmatic children with viral infections are admitted to hospital, and the chance of this happening may be determined by the degree of pre-existing bronchial hyper-reactivity. Seasonal variations in exposure to allergens may thus contribute to the underlying seasonal variations in asthma. This mechanism is consistent with the otherwise paradoxical finding that in August, a time of high exposure to allergens, asthma admissions are low,[3] whereas deaths from asthma are high.[6]

In conclusion, this retrospective study provides circumstantial evidence that admissions for asthma in children are mainly precipitated by viral infections, and that short term environmental factors seem to be comparatively unimportant.

We thank Douglas Blackmore and Linda Wadey for their help in arranging transfer of the data. JS was supported by a grant from the Royal Alexandra Hospital Centenary Appeal Fund.

References

[1] Khot A, Evans N, Lenney W. Seasonal trends in childhood asthma in south east England. *Br Med J* 1983;**287**:1257–8.

[2] Ashley JSA. Seasonal trends in childhood asthma. *Br Med J* 1983;**287**:1721.

[3] Khot A, Burn R, Evans N, Lenney C, Lenney W. Seasonal variation and time trends in childhood asthma in England and Wales 1975–81. *Br Med J* 1984;**289**:235–7.

[4] Sotomayor H, Badier M, Vervloet D, Orehek J. Seasonal increase of carbachol airway responsiveness in patients allergic to grass pollen. Reversal by corticosteroids. *Am Rev Respir Dis* 1984;**130**:56–8.

[5] McDonald MS, O'Driscoll BJ. Aerobiological studies based in Galway. A comparison of pollen and spore counts over two seasons of widely differing weather conditions. *Clin Allergy* 1980;**10**:211–5.

[6] Khot A, Burn R. Seasonal variation and time trends of deaths from asthma in England and Wales 1960–82. *Br Med J* 1984;**289**:233–4.

[7] Carlsen KH, Ørstavik I, Leegaard J, Høeg H. Respiratory virus infections and aeroallergens in acute bronchial asthma. *Arch Dis Child* 1984;**59**:310–5.

[8] Salvaggio J, Hasselblad V, Seabury J, Heiderscheit LT. New Orleans asthma. II. Relationship of climatologic and seasonal factors to outbreaks. *Journal of Allergy* 1970;**45**:257–65.

[9] Packe GE, Ayres JG. Asthma outbreak during a thunderstorm. *Lancet* 1985;**ii**:199–204.

[10] Salvaggio J, Seabury J, Schoenhardt EA. New Orleans asthma. V. Relationship between Charity Hospital admission rates, semiquantitative pollen and fungal spore counts, and total particulate aerometric sampling data. *J Allergy Clin Immunol* 1971;**48**:96–114.

[11] Anonymous. Asthma and the weather. *Lancet* 1985;**i**:1079–80.

[12] Tromp SW. Influence of weather and climate on asthma and bronchitis. *Review of Allergy* 1968;**22**:1027–44.

[13] Greenburg L, Field F, Reed JI, Erhardt CL. Asthma and temperature change. *Arch Environ Health* 1964;**8**:642–7.

[14] Blair H. Natural history of childhood asthma. 20 Year follow-up. *Arch Dis Child* 1977;**52**:613–9.

[15] Goodall JF. The natural history of common respiratory infection and some principles in its management. III. Wheezy children. *Journal of the College of General Practitioners* 1958;**1**:51–9.

[16] Dodge RR, Burrows B. The prevalence and incidence of asthma and asthma-like symptoms in a general population sample. *Am Rev Respir Dis* 1980;**122**:567–75.

[17] McIntosh K, Ellis EF, Hoffman LS, Lybass TG, Eller JJ, Fulginiti VA. The association of viral and bacterial respiratory infections with exacerbations of wheezing in young children. *J Pediatr* 1973;**82**:578–90.

[18] Mitchell I, Inglis JM, Simpson H. Viral infection as a precipitant of wheeze in children. *Arch Dis Child* 1978;**53**:106–11.

[19] Gardner PS, McQuillin J, Court SDM. Speculation on pathogenesis in death from respiratory syncytial virus. *Br Med J* 1970;**i**:327–30.

[20] Khan AU. The role of air pollution and weather changes in childhood asthma. *Ann Allergy* 1977;**39**:397–400.

[21] Carey MJ, Cordon I. Asthma and climatic conditions: experience from Bermuda, an isolated island community. *Br Med J* 1986;**293**:843–4.

[22] Greenburg L, Field F, Reed JI, Erhardt CL. Asthma and temperature change. II. 1964 and 1965 epidemiological studies of emergency clinic visits for asthma in three large New York City hospitals. *Arch Environ Health* 1966;**12**:561–3.

[23] Girsh LS, Shubin E, Dick C, Schlulaner FA. A study on the epidemiology of asthma in children in Philadelphia. *Journal of Allergy* 1967;**39**:347–57.

[24] Hobday JD, Stewart AJ. The relationship between daily asthma attendance, weather parameters, spore count and pollen count. *Aust NZ J Med* 1973;**3**:552–6.

[25] Hussain R, Norman PS, Marsh DG. Rapidly released allergens from short ragweed pollen. II. Identification and partial purification. *J Allergy Clin Immunol* 1981;**67**:217–22.

[26] Ordman D. An outbreak of bronchial asthma in South Africa affecting more than 200 persons caused by castor bean dust from an oil processing factory. *Int Arch Allergy Appl Immunol* 1955;**7**:10–24.

[27] Antó JM, Sunyer J. A point-source asthma outbreak. *Lancet* 1986;**i**:900–3.

[28] Anonymous. Soy kills in Barcelona. *New Scientist* 1987;**Sept 17**:32.

[29] Cockcroft DW, Ruffin RE, Dolovich J, Hargreave FE. Allergen-induced increase in non-allergic bronchial reactivity. *Clin Allergy* 1977;**7**:503–13.

Correspondence to Dr W Lenney, Royal Alexandra Hospital for Sick Children, Brighton BN1 3JN.

Accepted 18 July 1988

Archives of Disease in Childhood, 1989, **64,** 108–113

Lung function eight years after neonatal ventilation

B ANDRÉASSON,* M LINDROTH,* W MORTENSSON,† N W SVENNINGSEN,*
AND B JONSON‡

*Neonatal Intensive Care Unit, Departments of *Paediatrics and ‡Clinical Physiology, University Hospital, Lund, and †Department of Paediatric Radiology, St Göran's Hospital, Stockholm, Sweden*

SUMMARY Forty children who had had artificial ventilation during the neonatal period were studied at the age of 8–10 years with spirometry, the nitrogen washout test, bicycle exercise test, pulse oximetry, electrocardiogram, vectorcardiogram, and chest radiography. The median gestational age at birth was 29 weeks, and the median birth weight was 1310 g. Hyaline membrane disease was the indication for neonatal ventilation in 25 children. Bronchopulmonary dysplasia was diagnosed from radiographs in 11 infants (27%).

Airway obstruction was observed in 10 of 11 children who had had bronchopulmonary dysplasia and in nine of 29 children who had not. After inhalation of terbutaline, the forced expiratory volume in one second (FEV_1) was significantly increased. General hyperinflation was found in 16 of 17 children with abnormal chest radiographs (eight who had had bronchopulmonary dysplasia and nine who had not). Functional residual capacity was significantly higher in children with abnormal radiographs. Each child had a normal maximum working capacity and a normal electrocardiogram, and all but two had normal vectorcardiograms. Oxygen saturation at maximum work load decreased significantly in both groups of children. The risk of future respiratory problems calls for further follow up of lung function and chest radiography.

The long term effects on pulmonary function of ventilation during the neonatal period that have been reported are airways obstruction, bronchial hyper-reactivity, hyperinflation, and oxygen desaturation at maximum work load.[1–6] In our longitudinal follow up studies of preterm infants we have reported persistent radiographic lung abnormalities at 6 years of age in 10 of 14 children who had bronchopulmonary dysplasia as neonates.[7] When the children were old enough to cooperate satisfactorily in extended lung function studies (that is, at 8–10 years of age), we performed the present study that was designed to evaluate the long term association between ventilation of preterm infants in the neonatal period and later pulmonary function, chest radiography, and electrocardiography.

Patients and methods

During a two and a half year period 48 preterm infants weighing below 2500 g at birth survived neonatal diseases after treatment with pressure generated ventilation through a nasotracheal tube. The results of respiratory function tests carried out during infancy and at the age of 6 years have previously been reported.[7 8] One of the children died of the sudden infant death syndrome, four moved from the region, two refused to enter the present follow up study, and one could not do the tests because of tetraplegia. Clinical data on the remaining 40 children are shown in table 1.[9]

In the previous studies[7 8] the infants were divided into three groups based on the radiological findings soon after they were taken off the ventilators: normal; mild interstitial parenchymal abnormalities; and, bronchopulmonary dysplasia stages III or IV according to the classification of Northway.[10] In the present study the first two groups have been combined as group 1, and the third group becomes group 2. Bronchial asthma was present in other members of the families of two children in group 2 and four in group 1. There were habitual smokers in the families of five children in group 2 and 21 in group 1.

Lung function studies included vital capacity (VC) and forced expiratory volume in one second (FEV_1),

Table 1 *Clinical data about the children studied*

	Children in group 1 (n=29)	*Children in group 2 (n=11)*	*p Value**	*Group tested with terbutaline (n=16)*
Boys:girls	13:16	5:6	NS	6:10
Median (range) birth weight (g)	1380 (800–2480)	1030 (780–1400)	0·009	1180 (780–2480)
Median (range) gestational age (weeks)	29 (26–36)	28 (25–30)	0·05	28 (25–33)
No with hyaline membrane disease in neonatal period	16	9	NS	11
No with recurrent apnoea in neonatal period	7	2	NS	4
No with other disorders in neonatal period	6	0		1
Median (range) time spent on ventilator (days)	6 (2–72)	29 (13–59)	<0·001	22 (3–72)
Median (range) age at follow up (years)	9·2 (8·3–10·3)	8·6 (8·2–10·0)	NS	8·7 (8·2–10·0)
Median (range) standard deviation in height from predicted value for normal Swedish children[9]	−0·3 (−3·0 to 3·0)	−0·5 (−1·9 to 0·8)	NS	−0·1 (−3·0 to 3·0)
Median (range) standard deviation in weight from predicted value for normal Swedish children[9]	0 (−2·5 to 2·9)	−0·3 (−1·3 to 1·2)	NS	−0·1 (−2·5 to 2·9)

*Statistical analysis by Mann-Whitney U test.

which were measured with a Bernstein spirometer, and functional residual capacity (FRC), which was measured by the nitrogen washout method.

A progressive exercise tolerance test was carried out on a bicycle ergometer (Siemens Elema AB) according to the method of Godfrey *et al.*[11] The initial workload, 20–30 W depending on height, was increased by 10–15 W/minute until exhaustion. The electrocardiogram was recorded continuously. Oxygen saturation was measured in 33 children by pulse oximetry, and in 15 the signal was recorded on paper (Ohmeda Biox 3700 Pulse Oximeter).

Blood pressure, an electrocardiogram, and a vectorcardiogram[12] were recorded at rest in all children. The lung radiographs were taken in all children, except two who refused to participate. Radiographs were interpreted without knowledge either of clinical data or of the results of the lung function tests.

At a second visit the effects of a β_2 stimulating drug were tested in 16 of 20 children who were in group 2, or who had abnormal spirometry, or both (table 1). Four 0·5 mg doses of terbutaline were inhaled through a spacer at one minute intervals. FEV_1, VC, and FRC were measured before and 10 minutes after the inhalations.

Most data are presented as percentages of predicted values based on actual height.[11 13] Blood pressure at rest above the 97·5 centile was considered abnormal.[14]

For statistical analysis we used the Mann-Whitney U test, the Wilcoxon matched pairs signed rank test, Fisher's exact test, and the Spearman rank order correlation coefficient (r_s) test, all two tailed. Manual correction was made for ties of the Wilcoxon matched pairs test.

The study was approved by the ethics committee of Lund University, and informed consent was obtained from the parents for the participation of each child.

Results

CLINICAL DATA

Children in group 2 had lower birth weights, lower gestational ages, and longer periods of ventilation than the children in group 1 (table 1). The two groups did not differ in age, height, or weight at follow up.

Children with abnormal chest radiographs at follow up had been ventilated for longer than those with normal radiographs (p=0·002). The duration of ventilation for all children correlated with FEV_1 (r_s=−0·33, p=0·04) and VC (r_s=−0·35, p=0·04). The correlations between gestational age and birth weight and FEV_1 or VC did not reach significance, though gestational age and birth weight had been significantly lower in children who had abnormal chest radiographs at follow up (p=0·04 and p=0·02, respectively). There was no significant association between any respiratory function variable measured in the neonatal period and variables measured at follow up.

LUNG FUNCTION AND EXERCISE TESTING

FEV_1, FEV_1:VC, and FRC differed significantly from predicted values in both groups of children (table 2). The same variables were more abnormal among children in group 2 than children in group 1 (fig 1). Only one child in group 2 had normal spirometry. Abnormal FEV_1, FEV_1:VC, or both, were found in 12 girls and seven boys, including 10

Table 2 *Lung function tests*

	Children in group 1 (n=29)	*Children in group 2 (n=11)*	*p Value**	*Group tested with terbutaline (n=16)*
Median % of predicted FEV$_1$[13]	90†	75†	0·004	73
Median FEV$_1$:VC (%)	81†	74†	0·002	75
Median % of predicted VC	101	94	0·07	90
Median % of predicted FRC	121†‡	147†	0·06	139
Median % of predicted maximum working capacity	130†	134†	NS	127

*Statistical analysis by Mann-Whitney U test; †statistical analysis of Wilcoxon matched pairs signed rank test—difference between actual and predicted values $p<0·005$; ‡n=28.

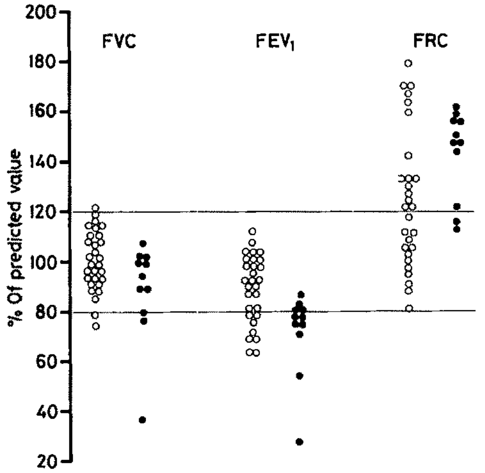


Fig 1 *Lung function 8–10 years later in children who had been on ventilators as neonates. VC, FEV$_1$, and FRC for each patient are expressed as percentages of values predicted for height.*[13] *Open circles denote children in group 1, solid circles those in group 2.*

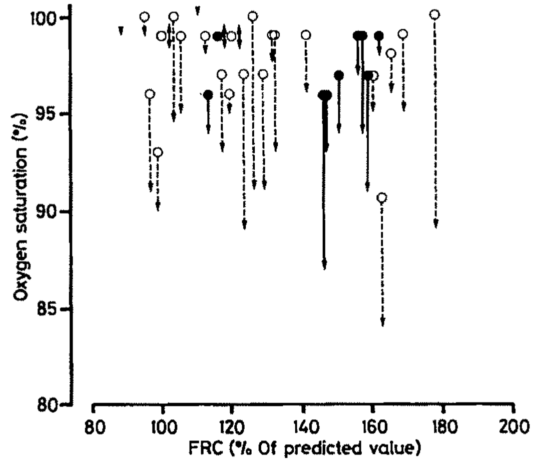


Fig 2 *Oxygen saturation at rest and during maximum work load and FRC. Open circles and broken lines denote children in group 1, and solid circles and thick lines those in group 2. Arrows show maximum workload.*

of 11 in group 2. FEV$_1$ correlated with VC ($r_s=0·78$, $p<0·001$), but not with FRC, or with oxygen saturation.

All children performed a normal maximum work load. The mean heart rate at maximum exercise was 184/minute, though three failed to reach a heart rate of 170/minute. There was no significant change in FEV$_1$ after work to exhaustion, in either group.

Oxygen saturation during work was significantly lower in both group 2 ($p=0·009$) and group 1 ($p=0·0004$), with a decrease of more than 4% in 11 of the 31 children tested (fig 2). Oxygen saturation was less than 95% during maximal exercise in 16 children; in two it was below 96% at rest (93 and 90·5%, respectively), decreasing during work to 90 and 84%, respectively. In all children, oxygen saturation increased again after exercise towards the pretest value, which was reached within four minutes in 11 of 18 children.

β SYMPATHOMIMETICS

After terbutaline inhalation FEV$_1$ increased significantly ($p=0·008$) (table 3). In five children in group 2 and four in group 1 the increase was over 10%. A

Table 3 *Change in the spirometric and lung volume reversibility effect of terbutaline 10 minutes after inhalation of 2 mg terbutaline in 16 children with BPD, impaired spirometry, or both*

Measurement	*% Change*		*p Value**
	Median	*Range*	
FEV$_1$	13	−6 to 33	0·008
FEV$_1$:VC	11	−6 to 32	0·001
VC	0	−5 to 19	NS
FRC	−3	−22 to 20	0·05

*Significance of differences before and after inhalation assessed by Wilcoxon matched pairs signed rank test.

decrease of FRC was noted in 14 of 16 children, but mean VC remained unchanged.

CHEST RADIOGRAPHY

Chest radiographs were abnormal in 17 (eight in group 2 and nine in group 1) of the 38 children examined (table 4). Abnormal pulmonary radiographs were significantly more frequent among children who had had abnormal radiographs just after they had been ventilated ($p<0{\cdot}001$). No cardiovascular abnormalities were found. Perihilar fibrosis was mild and had decreased during the four years preceding this study. Sixteen of 17 children with abnormal radiographs at this follow up had generalised hyperinflation (table 4). Four children in group 2 also had local areas of accentuated hyperinflation. In six children the degree of hyperinflation had increased during the four years preceding this study. FRC was above two standard deviations in 15 children, being higher in children with abnormal chest radiographs at follow up than in those with normal radiographs ($p=0{\cdot}04$). FRC was more often above 140% of the predicted value in children in group 2 than in those in group 1 ($p=0{\cdot}02$).

CARDIAC EXAMINATION

All children had normal electrocardiograms, both at rest and during exercise. Two children in group 2 had vectorcardiographic signs of right ventricular hypertrophy. After initial ventilator treatment for 24 and 58 days, respectively, they had extremely high respiratory resistance. One of them still had abnormal resistance at 1 year of age, but only slightly impaired lung function at 8 years of age (VC 89%, FEV_1 79%, and FRC 113% of predicted values). The other one had normal respiratory resistance at 2 years of age but lung function had deteriorated by 9 years of age (VC 75%, FEV_1 61%, and FRC 150% of predicted values). Mild hypertension (145/70) was diagnosed in one boy with unilateral renal agenesis, but all the other children had normal blood pressure at rest.

CLINICAL RESPIRATORY PROBLEMS

Six children, two in group 2, were treated with a β_2 stimulant during respiratory tract infections. After 4 years of age, one boy had been treated for pneumonia twice, and two children had been admitted to hospital for respiratory disorders—one once, the other twice. In one of them, a girl in group 2, histological examination of a biopsy specimen of nasal mucosa was compatible with the immotile cilia syndrome; she had persistent respiratory problems and deteriorated lung function (VC 35% and FEV_1 29% of predicted value).

Discussion

In our longitudinal follow up studies of preterm infants who had to be treated with artificial ventilation, we have shown that there is high respiratory resistance and low compliance in infancy after babies have been taken off the ventilators.[8] Most abnormal findings were found in infants in group 2. During the first two years the compliance normalised in all children, while resistance remained abnormal in half the children in group 2. Until 2 years of age bronchitis was frequent in children who had been treated on ventilators for more than two weeks, and especially in the children in group 2.[7] At 4–6 years of age, chest radiographs showed interstitial fibrosis and local areas of hyperinflation, again predominately in children in group 2. This follow up investigation at 8 to 10 years of age shows airway obstruction with general hyperinflation measured as abnormal FRC, and seen on chest radiographs.

The airway obstruction and hyperinflation seen in our children are similar to those seen in earlier studies of preterm infants treated with artificial ventilation and followed up at more than 5 years of age (Rutishauser M and Hug-Batscheler H. Presented at European Paediatric Respiratory Society VI meeting, Helsinki, 1987).[1 3–5 15–17] In some studies, in which the children examined had been more mature at birth, such abnormalities were either less pronounced[2 18–20] or did not differ from those in premature children born without lung disease.[4 6 21]

Confirming other reports,[17–20] the radiographs showed mild fibrosis and local hyperinflation. The predominant general hyperinflation found in our

Table 4 *Comparison between results of chest radiography in the neonatal period and those at 8–10 years of age*

Findings in the neonatal period after the child had been ventilated	*No of children*		*Findings at 8–10 years of age*		
			Normal	*Fibrosis*	*Hyperinflation*
Normal	20	(group 1)	17	0	3
Mild interstitial abnormalities	8		2	1	5
EPD stages III and IV[10]	10	(group 2)	2	5	8

patients has previously been reported in three preterm children aged 3 to 5 years.[22] It has also previously been seen in a long term follow up of children who had had tracheostomies during the first year of life.[23] The higher FRC seen in our children with hyperinflation emphasises the significance of this radiographic observation.

In contrast to our findings in group 2, signs of right ventricular hypertrophy have previously been reported in 30–70% of children with bronchopulmonary dysplasia.[5 17 24]

The effects of β_2 sympathomimetic drugs have previously been reported to vary in children with bronchopulmonary dysplasia[3 5] but we noted a positive effect in patients with bronchopulmonary dysplasia or abnormal spirometry, or both.

The observed super normal maximum working capacity probably represents normal maximum working capacity. According to our experiences of routine progressive exercise tests, Swedish children today exceed the normal values of British children 20 years ago.[11] Although lung function and chest radiographs were more abnormal in children in group 2 than in group 1, the maximum working capacity did not differ between the two groups. The significant decrease in oxygen saturation during exercise in both groups was similar to that observed by others.[19 25] Further interpretation of our results will require additional studies.

The absence of exercise induced bronchospasm in our children differs from the results of other investigators, who reported exercise induced bronchospasm in children with bronchopulmonary dysplasia,[1] as well as bronchial hyper-reactivity diagnosed with metacholine or histamine tests (Rutishauser M and Hug-Batschelet H. Presented at European Paediatric Respiratory Society VI Meeting, Helsinki, 1987).[2 5]

Contrary to the report of Nickerson and Taussig,[26] but in agreement with Gerhardt *et al*,[27] we found no correlation between bronchopulmonary dysplasia and family history of asthma. Our figures were the same as those reported by Riedel[2] in children with bronchopulmonary dysplasia but lower than that observed by Stahlman *et al* among children with hyaline membrane disease.[18]

In the children in our study the incidence of abnormal chest radiographs shortly after they had been taken off ventilators,[7 8] was associated with the occurrence of abnormal chest radiographs at follow up. It seems that the frequency of late radiographic changes are as common in the group of infants with initially mild interstitial abnormalities as in those with bronchopulmonary dysplasia. Our observations correspond to other reports in that we are able to correlate the length of time spent on the ventilator and the occurrence of an abnormal chest radiograph, and a low FEV_1 at late follow up (Rutishauser M and Hug-Batschelet H. Presented at European Paediatric Respiratory Society VI Meeting, Helsinki, 1987).[18] Radiographic changes at follow up also correlated with low birth weight and low gestational age.

Previously only one group has reported an association between neonatal and late lung function—that is, the development of severe airway obstruction at 9 years of age in three children with large FRC and low compliance in infancy.[5] We found high respiratory resistance in the neonatal period and persisting airway obstruction at 8 to 10 years in our children with both mild and severe neonatal lung disease. These observations support previous suggestions that not only degree of prematurity and severity of neonatal lung disease but also duration and probably mode of treatment by ventilator contribute to impaired airway development.[6 28]

In conclusion, most of our children had no regular respiratory disorders at 8 to 10 years of age. Our findings of airway obstruction, hyperinflation, and impaired oxygenation during exercise, however, as possible long term effects of neonatal ventilation, may imply a certain risk of future respiratory dysfunction. We therefore plan a pulmonary function and radiographic follow up of the same series in the teenage period. The beneficial effect of β_2 sympathomimetics on airway obstruction suggests bronchodilator treatment to be an alternative worth consideration during airway infection.

The work was supported by the Swedish Medical Research Council (grants 4732 and 02872), the Swedish National Association against Chest and Heart Diseases, "Stiftelsen Samariten", "Stiftelsen Allmänna BB:s Minnesfond" and "Förenade Liv" Mutual Group Life Insurance Company, Stockholm, Sweden.

References

[1] Bader D, Ramos AD, Lew CD, Platzker ACG, Stabile MW, Keens TG. Childhood sequelae of infant lung disease: exercise and pulmonary function abnormalities after bronchopulmonary dysplasia. *J Pediatr* 1987;**110**:693–9.

[2] Riedel F. Long term effects of artificial ventilation in neonates. *Acta Paediatr Scand* 1987;**76**:24–9.

[3] Berman W, Katz R, Yabek SM, Dillon T, Fripp RR, Papile L-A. Long-term follow up of bronchopulmonary dysplasia. *J Pediatr* 1986;**109**:45–50.

[4] Bertrand J-M, Riley SP, Popkin J, Coates AL. The long-term pulmonary sequelae of prematurity: the role of familial airway hyper-reactivity and the respiratory distress syndrome. *N Engl J Med* 1985;**312**:742–5.

[5] Smyth JA, Tabachnik E, Duncan WJ, Reilly BJ, Levison H. Pulmonary function and bronchial hyperreactivity in long-term survivors of bronchopulmonary dysplasia. *Pediatrics* 1981;**68**: 336–40.

[6] Coates AL, Bergsteinsson H, Desmond K, Outerbridge EW, Beaudry PH. Long-term pulmonary sequelae of premature birth with and without idiopathic respiratory distress syndrome. *J Pediatr* 1977;**90**:611–6.

[7] Lindroth M, Mortensson W. Long-term follow-up of ventilator treated low birthweight infants. I. Chest X-ray, pulmonary mechanics, clinical lung disease and growth. *Acta Paediatr Scand* 1986;**75**:819–26.

[8] Lindroth M, Jonson B, Svenningsen NW, Mortensson W. Pulmonary mechanics, chest X-ray and lung disease after mechanical ventilation in low birthweight infants. *Acta Paediatr Scand* 1980;**69**:761–70.

[9] Karlberg P, Taranger J, Engström I, *et al.* I Physical growth from birth to 16 years and longitudinal outcome of the study during the same age period. *Acta Paediatr Scand* 1976;**65**(suppl 258):7–76.

[10] Northway WH, Rosan RC, Porter DY. Pulmonary disease following respiratory therapy of hyaline-membrane disease. *N Engl J Med* 1967;**276**:357–68.

[11] Godfrey S, Davies CTM, Wozniak E, Barnes CA. Cardiorespiratory response to exercise in normal children. *Clin Sci* 1971;**40**:419–31.

[12] Jonson B, Almquist L-O, Edenbrandt L, Lundh B, Niklason L, Pahlm O. High quality vectorcardiography. In: *Proceedings of computers in cardiology, September 88–11, 1985, Linköping, Sweden.* Washington: Institute of Electrical and Electronics Engineers, 1985:163–6.

[13] Polgar G, Promadhat V. *Pulmonary function testing in children: techniques and standards.* Philadelphia: WB Saunders, 1971.

[14] Blumenthal S, Epps RP, Heavenrich R, *et al.* Report of the task force on blood pressure control in children. *Pediatrics* 1977; **59**(suppl):797–804.

[15] Wheeler WB, Castile RG, Brown ER, Wohl MEB. Pulmonary function in survivors of prematurity. *Am Rev Respir Dis* 1984;**129**:218.

[16] Borkenstein J, Borkenstein M, Rosegger H. Pulmonary function studies in long-term survivors with artificial ventilation in the neonatal period. *Acta Paediatr Scand* 1980;**69**:159–63.

[17] Johnson JD, Malachowski NC, Grobstein R, Welsh D, Daily WJR, Sunshine P. Prognosis of children surving with the aid of mechanical ventilation in the newborn period. *J Pediatr* 1974;**84**: 272–6.

[18] Stahlman M, Hedvall G, Lindström D, Snell J. Role of hyaline membrane disease in production of later childhood lung abnormalities. *Pediatrics* 1982;**69**:572–6.

[19] Heldt GP, McIlroy MB, Hansen TN, Tooley WH. Exercise performance of the survivors of hyaline membrane disease. *J Pediatr* 1980;**96**:995–9.

[20] Lamarre A, Linsao L, Reilly BJ, Swyer PR, Levison H. Residual pulmonary abnormalities in survivors of idiopathic respiratory distress syndrome. *Am Rev Respir Dis* 1973;**108**: 56–61.

[21] Mansell AL, Driscoll JM, James LS. Pulmonary follow-up of moderately low birth weight infants with and without respiratory distress syndrome. *J Pediatr* 1987;**110**:111–5.

[22] Shepard FM, Johnston RB, Klatte EC, Burko H, Stahlman M. Residual pulmonary findings in clinical hyaline-membrane disease. *N Engl J Med* 1968;**279**:1063–71.

[23] Haglund G, Bjure J, Claesson I, *et al.* Long-term follow-up of infants under intensive care with tracheotomy during the period 1956–1965. *Acta Anaesthesiol Scand* 1984;**28**:166–73.

[24] Harrod JR, L'Heureux P, Wangensteen OD, Hunt CE. Long-term follow-up of severe respiratory distress syndrome treated with IPPB. *J Pediatr* 1974;**84**:277–86.

[25] Sheller J, Lucht W, Goel A, Snell J, Stahlman M. Pulmonary function in long term survivors of hyaline membrane disease. *Am Rev Respir Dis* 1986;**133**:154.

[26] Nickerson BG, Taussig LM. Family history of asthma in infants with bronchopulmonary dysplasia. *Pediatrics* 1980;**65**:1140–4.

[27] Gerhardt T, Hehre D, Feller R, Reifenberg L, Bancalari E. Serial determination of pulmonary function in infants with chronic lung disease. *J Pediatr* 1987;**110**:448–56.

[28] Tepper RS, Morgan WJ, Cota K, Taussig LM. Expiratory flow limitation in infants with bronchopulmonary dysplasia. *J Pediatr* 1986;**109**:1040–6.

Correspondence to Dr Bengt Andréasson, Department of Paediatrics, University Hospital, S-221 85 Lund, Sweden.

Accepted 5 July 1988

Archives of Disease in Childhood, 1989, **64,** 114–118

Staff stress and job satisfaction at a children's hospice

H WOOLLEY,* A STEIN,† G C FORREST,* AND J D BAUM‡

**Park Hospital for Children, Oxford, †Department of Psychiatry, University of Oxford, Warneford Hospital, and ‡Institute of Child Health, Royal Hospital for Sick Children, Bristol*

SUMMARY A study of staff stress and job satisfaction was undertaken in a children's hospice. In addition factors were investigated which might be stressful or which helped staff to manage in difficult circumstances. Three quarters were under comparatively little stress and in general showed very few psychological symptoms but a distinct subgroup were under a great deal of stress. A number of factors, notably recent personal bereavement and unresolved grief about a death that had occurred before they came to work at the hospice, distinguished this small group. Job satisfaction was generally high.

The main sources of stress were: the sense of impotence staff felt when they were unable to relieve perceived needs or distress; dealing with negative responses in families, and conflicts within the staff group. The most important mitigating factors were: the informal support that staff provided for each other in this small cohesive working unit, the homelike atmosphere of the hospice, and the diversity of professional and personal skills among the staff group. The implications of these findings for reducing stress among staff dealing with dying people are discussed; this includes not only staff on paediatric wards, intensive care and neonatal units, but also community paediatric nurses.

Medical concern for people in occupations that impose unusual degrees of stress is not a new phenomenon. There has recently been an increasing interest in the care of the terminally ill together with a growing recognition that staff working with the dying and their families may experience particular stress. Initial studies were concerned with staff in intensive care units[1] and special care baby units.[2] Subsequent studies focused on those caring for dying adults,[3–8] and most recently on staff caring for dying children and their families.[9 10]

Vachon[7] argues that there are a number of reasons why staff working with terminally ill patients are especially at risk. For example, such work may attract staff with high ideals who are in danger of entertaining unrealistic expectations; constant confrontation with death may evoke unresolved past losses and cause grief reactions or unrecognised and unacknowledged depression, and regular contact with death can diminish ordinary relationships and have an adverse effect on friendships, marriages, and family life. Vachon also found that certain personality problems, as well as close identification with individual patients, were associated with a lot of stress. Lattanzi[10] noted the emotional stress for staff arising from the sense of powerlessness associated with being unable to save the life of a dying child or eliminate the pain of bereavement.

Maguire[8] pointed out that there are communication problems in dealing with patients who are terminally ill, and in particular noted the use of distancing tactics by staff. For example, cues from patients may be ignored, and patient distress minimised by such tactics as inappropriate cheerfulness and premature or false reassurance.

The first children's hospice in the United Kingdom was opened in 1982 and provided an opportunity to investigate some of the issues raised above. This hospice, the nature and evolution of which has been described elsewhere,[11] offers respite and terminal care as a home away from home for children suffering chronic life threatening and terminal illnesses. The most common illnesses among children in this hospice are a wide range of neurodegenerative and metabolic disorders, muscular dystrophy, and a small group with neoplasms predominantly of the central nervous system. The hospice is a purpose built eight bedded unit and has space to accommodate families and children.

The aims of our study were to examine: firstly, the degree of stress experienced by staff caring for children and their families; secondly, those factors which staff found stressful, and those which helped them to manage in difficult circumstances; thirdly, degrees of, and factors associated with, job satisfaction.

Subjects and methods

At the time of the study 27 staff were employed at the hospice for the direct care of the children and their families. This care included sharing all domestic duties such as washing, cleaning, shopping, and cooking. Of the 27 staff, 24 took part in the study, two declined, and one was on sick leave. Of the 24 staff interviewed, ages ranged from 22–55 years, 14 being between 30 and 40. Four staff lived on their own, 19 with partners, and one with parents. There were only two men. Sixteen worked full time and eight part time, five of the latter working only on night shifts. Twelve were qualified nurses (RSCN), five had qualifications in teaching, physiotherapy, or social work, and six had no formal qualifications. There was one general practitioner who served the hospice and was attached to a local group practice.

The assessment entailed interviewing each member for about one and a half hours during which a semistructured questionnaire was given and the staff were asked to complete Goldberg's 60 item general health questionnaire.[12] The general health questionnaire (a well established self report questionnaire[13]) measures psychological symptoms, in particular somatic symptoms, anxiety and insomnia, social dysfunction, and severe depression. A score of 11 is generally taken as the cut off point above which the number of symptoms is considered significant. General health questionnaire scores[5] were used together with the amount of time that staff spent on sick leave, and the turnover rate of staff as indices of stress. Job satisfaction was assessed by a seven point rating scale with four being the mode, one indicating little, and seven indicating a great deal of satisfaction.

The semistructured questionnaire was used to investigate a variety of aspects of hospice life; subjects were asked what led to job satisfaction, what they found stressful, and what mitigated stress in the following areas: different types of illness, specific symptoms, and death of a child; factors relating to families of children; personal characteristics and circumstances that helped or hindered them; layout and organisation of the hospice; and staff support and training.

At the end of the interview a clinical assessment was made by the interviewer of the extent of unresolved grief concerning a death of a relative or friend that had occurred more than a year previously, and before beginning work at the hospice. This was assessed by taking into account a high degree of expressed emotion, together with immediacy of recall and the lack of an apparent blunting of emotion with time when discussing the deceased person.

Results

INDICES OF STRESS

The general health questionnaire scores ranged from 0–39 with 18 (75%) staff scoring below the cut off point of 12 (range 0–9; median 3) and six (25%) scoring above that point (range 19–39; median 33) (table 1). Thus a distinct group with high general health questionnaire scores was identified.

The main symptoms among the high scorers (table 2) were anxiety and insomnia, and to a lesser degree somatic symptoms and social dysfunction. Symptoms of depression were rarely reported. When asked about death among family and friends (table 3), four out of the six high scorers on the general health questionnaire compared with three of the 18 low scorers reported loss in terms of the death of a close relative or friend in the preceding year (Fisher's test of exact probability <0·05).

On clinical assessment, four of the high scorers showed substantial unresolved grief, compared with

Table 1 *Staff scores on Goldberg's general health questionnaire*

General health questionnaire score	*No of staff*
0	7
1	1
2	2
3	3
5	1
8	2
9	2
19	1
21	1
31	1
34	1
37	1
39	1

Table 2 *General health questionnaire subscores*

	Mean No in each group	
	High scores (n=6)	*Low scores (n=18)*
Somatic symptoms	4	1
Anxiety and insomnia	6	1
Social dysfunction	3	0
Severe depression	1	0

Table 3 *Deaths of relatives, close friends, and unresolved grief, and general health questionnaire scores*

	High general health questionnaire scores (n=6)	*Low general health questionnaire scores (n=18)*
Death of first degree, close second degree relative, or close friend during past year	4	3*
Unresolved grief: death of relative in past that still evoked current distress	4	1**
Death of a relative or close friend over past year, or unresolved grief, or both	5	3**

*p<0·05, **p<0·01 (Fisher's test of exact probability).

only one low scorer (Fisher's test of exact probability <0·05). In total, five of six high scorers had lost a relative or close friend in the past year or showed substantial unresolved grief, or both, compared with only three out of 18 low scorers. (Fisher's test of exact probability <0·01).

Each member of staff had an average of 6·2 days sick leave a year. This compared with an average of 11·5 days sick leave a year for nursing staff on nine paediatric wards in South London (M Rose, unpublished observations). Twenty one (88%) had worked at the hospice for more than two years, 13 (54%), since it opened four years before this study, and three (12%) had worked there for less than two years.

JOB SATISFACTION RATING

On the seven point rating of current job satisfaction staff scores ranged from 3–7 with a median of 6. Staff reported that their satisfaction with the job remained high despite experiencing of times of great stress.

STRESSFUL AND MITIGATING FACTORS IN HOSPICE LIFE

Different types of illness, specific symptoms, and death of a child. Many staff said that it was not so much the particular illness that upset them but symptoms or behaviour that seemed uncontrollable. Uncontrollable symptoms created much stress while the ability to relieve a symptom or distress was extremely rewarding. Witnessing a child's pain was rated by 20 staff (83%) as the most stressful aspect, and perceiving a child's mental distress was a close second for 15 staff.

A number of conditions were found to be stressful for different reasons. Eight (33%), found the neurodegenerative disorders particularly distressing because of the slow diminishing quality of life, and the effect on the family. Five (20%) found muscular dystrophy in teenagers distressing because of the increasing physical deterioration in the presence of intact intellectual faculties. A further five found the neoplastic conditions distressing, because cancer was seen as a disease that their own families were more likely to suffer from. At the same time, however, staff often gained satisfaction from performing specific tasks (for example, giving pain relief) which comforted patients.

Staff felt particularly stressed by an expected death that did not occur, with all its attendant uncertainty and unpredictability. Furthermore, not being directly involved (that is, not being the primary carer) was difficult for staff who had been close to child and family; as one said 'to merely observe is to be impotent'. Staff felt that they too needed an opportunity for parting and the rituals of separation.

Factors related to the families of children. A number of factors were reported by staff to be especially difficult to manage. In particular, 10 (42%) found it difficult to cope with certain negative responses of families, especially anger (hidden or overt), helplessness, and the occasional criticism of staff. Grieving relatives who did not share or show their grief (particularly some fathers and grandparents) left staff members uncertain as to how to relate to them, and therefore feeling helpless. A third of the staff reported identifying closely with individual parents or children, particularly if the parent was a similar age to the staff member or the children were similar in age or in some other way to their own children.

Personal characteristics and circumstances which helped or hindered staff. Within the hospice, 19 (80%) staff reported that difficulties in staff communication and inter-relationships were an important source of stress. Conversely, all staff felt that informal staff support was the most important factor which helped them to cope.

Staff indicated that having a sense of humour, knowing one's own limitations and what skills one had to offer, having a philosophy of life that helped them through good and bad times, as well as having supportive friends and relations, were the most important factors enabling them to function effectively at work. Factors which created some difficulty were balancing home and work commitments, cutting off at the end of the day and allowing themselves time off, and having enough energy for friends and family. Some staff struggled with the problem of how to avoid making the ordinary events in life seem trivial and banal in the face of the serious life and death events of the hospice.

Layout and organisation. All the staff emphasised how much they valued the hospice's informal homelike quality. Sharing of domestic duties and decisions brought them closer together, and enhanced the mutual support and friendship within the team which they cited as a crucial ingredient of job satisfaction. Staff valued the lack of a rigid hierarchy and red tape.

The general consensus was that catering for a maximum of eight resident children at any one time together with accompanying relatives (this could involve 20 or more people at a time) was the upper manageable limit. As one member of staff commented 'we are in danger of losing the cohesive family like personal care atmosphere once we have more people than can sit comfortably around the (large circular) dining table'.

Staff valued having time to share with families and colleagues, especially to enable them to respond to individual needs and to continue the child's preferred personal routine.

Staff support and training. All staff said that informal staff support was the most important factor in helping them to cope with the work they faced. Half the staff regularly attended each of the two weekly staff group meetings; of these 60% found the regular staff business meetings helpful, and 80% valued the support group meeting with a visiting consultant psychiatrist. Several staff commented that such meetings could be uncomfortable and even painful at times, but noted that enjoyment was quite different from usefulness and the sessions that tackled the more difficult and uncomfortable issues often proved the most helpful in the long run. Seventeen (70%) carers drew strength from religious beliefs, but this support stemmed more from personal convictions such as belief in an after life than from formal religious connections.

While staff valued their professional qualifications, they particularly identified the contribution of life experience in equipping and helping them to meet the varied demands of their work.

Discussion

Our findings suggest that at this hospice comparatively few of the staff experienced high degrees of stress but the importance of the 25% who did should not be underestimated in view of the nature of the work. Specific factors concerning recent personal bereavement and unresolved grief from the past distinguished this small group of high general health questionnaire scorers from the rest of the staff. Although the total number of subjects was comparatively small, the findings have some general implications for both staff selection and staff support along the lines of previous recommendations.[8 9] In particular when selecting staff it is important to be alert to the possible vulnerability of potential staff carrying unresolved grief, as great distress can be rekindled when a current trigger event echoes back to and resurrects a sense of loss. Furthermore, specific consideration and support needs to be given to staff who experience current personal bereavement. The very nature of the work serves as a constant reminder of their loss, and may interfere with their own natural grieving. In particular, counselling and additional time off may be necessary.

The staff were able to pinpoint a number of important issues which they found stressful. Firstly, when staff felt unable to relieve perceived needs, symptoms, or distress it left them feeling helpless. Thus when appointing staff it may be important to look for qualities of understanding and strength that will enable a staff member to live with another's distress without feeling too diminished by a sense of helplessness.[14]

Secondly, the negative attitudes of some families which manifested as anger or criticisms often made staff uncertain how they should react and left them feeling undermined and distressed. It seems essential that a good hospice support system needs to be fostered together with special training to aid the staff in understanding human responses and to prevent them inadvertently resorting to the distancing tactics described by Maguire.[8] Staff may also need help in avoiding inappropriate overinvolvement with family members.

Thirdly, problems with relationships within the staff group could be an important source of stress. Overall it seems that the cohesiveness of the staff group in such a small hospice is an important source of coping and therefore of stress when cohesiveness is threatened by inter staff conflict. As Mount and Voyer[15] point out, however, any group claiming to work as a team should show their battle scars: 'if they don't have scars they haven't worked as a team.'

The staff were able to identify a number of issues which they found helpful, supportive, and rewarding. These included the existence of supportive interpersonal staff relationships, the homelike physical environment, and the diversity of professional and personal skills among the staff group. The ability to meet and relieve distress or any perceived need was repeatedly emphasised by staff as important for job satisfaction, just as an inability to do so led to staff feeling stressed.

Outside the hospice, staff felt they needed the support of family or friends and enough time off to enjoy outside interests in order to maintain a balanced perspective at work. Furthermore, they needed time and space both in and out of work to come to terms with important events they had witnessed, such as death and the stress experienced by families.

Two caveats should be mentioned when drawing our conclusions. Firstly, the comparatively small number of staff (24) limits our conclusions, although our findings are buttressed by their consistency with other studies. Secondly, the nature of this hospice's evolution together with the continued inspiration and involvement of a charismatic founder adds a unique quality to the hospice and its life.

The findings of this study have implications for groups of staff caring for terminally ill children, including those on paediatric wards, neonatal and intensive care units. Together with the recent upsurge of interest in children's hospices, however, there has been a concurrent movement towards caring for the dying child at home. Should this become a greater trend the issues raised by this study will need to be tackled in the community. For instance, a community paediatric nurse would need a base where he or she could draw support and understanding to help cope with the stress inherent in the work. Thus while some families may prefer their children to be cared for at home, the nurse may find it more difficult. These are issues which may need to be considered by educators in the field especially those concerned with paediatric nurse training.

We are particularly grateful to the staff of Helen House who so generously took part in this study. We also thank Pavlos Anastasiades, Carolyn Fordham, Pepe Catalan, Peter Maguire, Ann Day and Sylvia Rhys for their help, and the DHSS who funded the study.

References

[1] Vreeland R, Ellis GL. Stress on the nurse in an intensive care unit. *JAMA* 1969;**208**:332–4.

[2] Price ME. Why NICU nurses burn out and how to prevent it. *Contemporary Obstetrics and Gynecology* 1979;**13**:37–46.

[3] Vachon MLS. Motivation and stress experienced by staff working with the terminally ill. *Death Education* 1978;**2**:113–22.

[4] Vachon MLS, Lyall WAL, Freeman SJJ. The measurement and management of stress in health professionals working with advanced cancer patients. *Death Education* 1978;**1**:365–75.

[5] Lyall A, Vachon MLS, Rogers J. A study of the degree of stress experienced by professionals caring for dying patients. In: Ajemian I, Mount BM, eds. *The Royal Victoria Hospital manual on palliative/hospice care.* New York: Arno Press, 1980:498–509.

[6] Vachon MLS. Support systems for the health professional. *Proceedings of the American Cancer Society fourth national conference on human values and cancer.* New York: American Cancer Society, 1984:89–93.

[7] Vachon MLS. *Occupational stress in the care of the critically ill, the dying, and the bereaved.* Washington: Hemisphere Publishing Corporation, 1987.

[8] Maguire P. Barriers to psychological care of the dying. *Br Med J* 1985;**291**:1711–3.

[9] Vachon MLS, Pakes E. Staff stress in the care of the critically ill and dying child. In: Wass H, Corr CA, eds. *Childhood and death.* New York: Hemisphere Publishing, 1984:151–82.

[10] Lattanzi ME. An approach to caring: caregiver concerns. In: Corr CA, Corr MC, eds. *Hospice approaches to pediatric care.* New York: Springer Publishing, 1985:261–77.

[11] Dominica F. Helen House: a hospice for children. In: Corr CA, Corr MC, eds. *Hospice approaches to pediatric care.* New York: Springer Publishing, 1985:107–25.

[12] Goldberg D. *Manual of the general health questionnaire.* Slough: National Foundation for Education Research, 1978.

[13] Goldberg D. *The detection of psychiatric illness by questionnaire.* London: Oxford University Press, 1972.

[14] Dominica F. Reflections on death in childhood. *Br Med J* 1987;**294**:108–10.

[15] Mount BM, Voyer S. Staff stress in palliative hospice care. In: Ajemian I, Mount BM, eds. *The Royal Victoria Hospital manual on palliative/hospice care.* New York: Arno Press, 1980:446.

Correspondence to Mrs H Woolley, Park Hospital for Children, Headington, Oxford OX3 7LQ.

Accepted 13 July 1988

Archives of Disease in Childhood, 1989, **64,** 119–123

Totally implantable venous access systems in paediatric practice

A ESSEX-CATER,* J GILBERT,† T ROBINSON,† AND J M LITTLEWOOD†

**Regional Paediatric Oncology Unit, Seacroft Hospital, Leeds and †Regional Cystic Fibrosis Unit, St James's University Hospital, Leeds*

SUMMARY Forty seven totally implantable venous access systems have been inserted in 45 patients for the management of malignant disease (n=29), haematological disorders (n=5), and cystic fibrosis (n=11). We report our experience with them and discuss the problems we have encountered during the past three years.

If children require repeated or prolonged venous access it is accepted that long tunnelled lines improve the patients' quality of life and reduce the risk of thrombophlebitis.[1] Infection of such lines is common, however,[2] and even when they are not in use certain activities must be curtailed (for example, swimming), and frequent flushing of the line is needed to prevent blockage. Totally implantable systems are now available that reduce these problems.[3] We have made increasing use of these systems during the past three years, and have implanted 47 in 45 children attending the regional oncology unit (n=34) and regional cystic fibrosis unit (n=13).

Patients and methods

Between August 1984 and January 1988, 47 totally implantable systems (46 Port-A-Cath (Pharmacia) and one Implantofix (Braun Medical)) were inserted in 45 patients. There were 18 boys and 27 girls and age at insertion ranged from 0·7 to 20 years (mean 7·9). Twenty children were less than 5 years of age. Twenty nine children were being treated for malignant disease (25 with solid tumours and four with leukaemia). Eleven had cystic fibrosis, two had thalassaemia, two had aplastic anaemia, and one had congenital red cell aplasia.

The systems were inserted for intensive or prolonged chemotherapy, repeated courses of antibiotics, or repeated blood transfusions in patients with poor venous access. Implantable systems were used if children had previously tampered with long indwelling lines or if it was thought the family would have difficulty coping with daily aseptic flushing of a tunnelled line. They were also placed in older children who did not want the more conspicuous tunnelled line and in patients where their use was likely to be intermittent (such as those with cystic fibrosis) and where daily flushing would be inconvenient and might increase the risk of infection.

The systems have been used for blood sampling, antimicrobial and cytotoxic chemotherapy, infusion of blood products, parenteral nutrition, and continuous infusion of opiates during terminal care. Though the systems have been used primarily in hospital, three have been used at home. Two children with cystic fibrosis have received a total of 14 courses of antimicrobial treatment at home, and a patient with cancer has received infusions of opiates. Patients and relatives have been taught to manage the devices successfully at home with the support of the cystic fibrosis sister (TR), permitting more regular courses of antimicrobials to be given with the least possible interference with home and school life.

INSERTION

All except one of the catheters were implanted by one of three paediatric surgeons. The catheter was inserted into the internal jugular or subclavian vein and the tip positioned in the superior vena cava. It was then tunnelled to the site of the subcutaneous pocket in which the portal was placed. The portal was then connected to the catheter and sutured in place (fig 1). The procedure was carried out under general anaesthesia except for one case, in which the system was fully replaced (in a child with cystic fibrosis) under sedation and local anaesthesia.

At first in the patients with cancer the systems were implanted on the chest wall above the nipple; more recently most have been sited below the

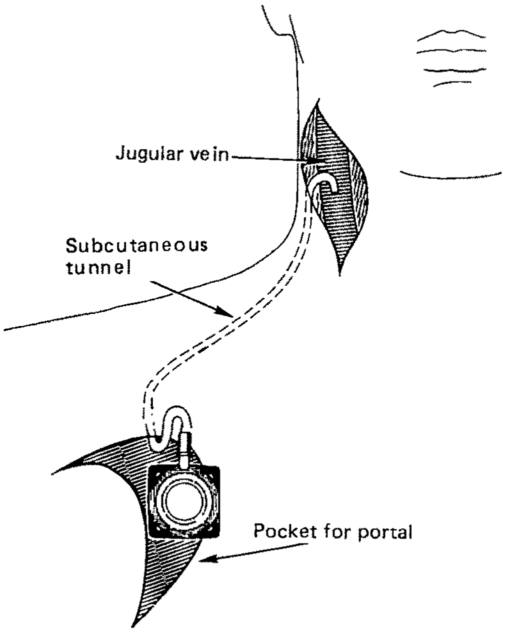


Fig 1 *Insertion of Port-A-Cath.*

nipple. In older girls the systems should be sited away from the breasts and the area covered by the bra, and in children with cystic fibrosis the chosen site should not interfere with chest physiotherapy. The position should be decided after discussions between the patient, parents, surgeon, and physiotherapist. In older patients who might operate their systems themselves, they should be placed in an accessible position, and away from the sensitive area round the nipple. They should be sited outside the area of any planned radiotherapy field.

USE AND MAINTENANCE

The system consists of a subcutaneous portal with a self sealing septum attached to a central venous catheter (fig 2). When in place they are totally subcutaneous and access to the portal is by a non-coring Huber needle. If an ordinary needle is used it will remove a core from the septum which will then leak. Correctly used the system will tolerate at least 1000 to 2000 perforations, depending on the size of needle used.

Insertion of the needle is done aseptically and is preceded by scrubbing an area up to three inches round the portal site for three minutes with povidone iodone solution. After palpation of the portal the needle is inserted into the septum at 90° until it touches the base plate. It is important that when the needle is withdrawn the portal is held in place and positive injection pressure is maintained to prevent reflux of blood into the catheter; a closed system must be maintained at all times.

When not in use the systems must be flushed every three to four weeks using 5 ml of heparinised saline (100 units heparin/ml). When in use a 90° needle attached to an extension tube and three way tap should be used. The systems are flushed as the needles are removed.

Particular care must be taken to avoid mixing fluids that may cause a precipitate to be deposited in the system. After drawing blood the system should be flushed immediately with 2 ml heparinised saline and then 20 ml of 0·9% saline injected before the final 5 ml of heparinised saline as the needle is removed.

In no patient has the skin overlying the portal site been denervated. In elective procedures, if the child requests it, we apply an anaesthetic cream to the portal site at least one hour before inserting the needle.

Most of the children are active during their infusions and occasionally needles are dislodged. This has not resulted in blockage of the system even if time was permitted for anaesthetic cream to be used before the needle was resited. In patients with cystic fibrosis exercise and activity are an important part of treatment and a heparin lock using a solution of 100 units/ml may be used to permit freedom from the infusion during courses of treatment.

When in use for patients with cancer the skin over the portal was cleaned daily with povidone iodine solution and povidone iodine soaked gauze was placed over the entry site of the needle. This tended to dry the skin and stain the clothing, so we used

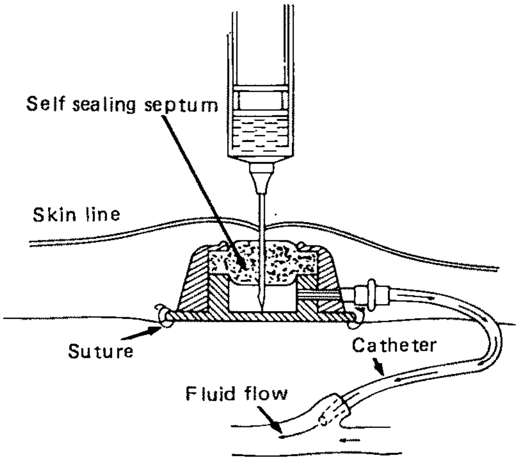


Fig 2 *Access to the Port-A-Cath.*

chlorhexidine gluconate cream on the gauze rather than povidone iodine. More recently we used dry dressings that were changed each day. The needle was changed every five days.

Because patients with cystic fibrosis are not immunocompromised a different regimen of dressing and cleansing the needle site evolved. A dry dressing under an adhesive membrane was used and this was only changed when the needle was replaced (every seven days).

The systems were operated only by nurses or doctors familiar with them, or parents or older patients who were trained to use them.

Eight children were neutropenic (neutrophil concentration less than $1{\cdot}0\times10^9/l$), five were thrombocytopenic (platelet concentration less than $100\times10^9/l$) and one had deranged coagulation (international normalised ratio 1·5, kaolin cephalin clotting time 70 seconds) at the time of insertion. All thrombocytopenic patients received perioperative transfusions of platelets. The child with deranged coagulation and thrombocytopenia received intravenous vitamin K and fresh frozen plasma in addition to the transfusions of platelets.

The patients with cystic fibrosis were given prophylactic antibiotics intravenously and intensive physiotherapy starting about a week before insertion of the system, and this treatment was continued afterwards until their lung function had returned to preoperative capacity. Prophylactic antibiotics were not routinely used for other patients even if they were neutropenic. Two children were already being treated with antibiotics intravenously at the time of insertion because of fever associated with neutropenia. Three patients were given short courses of antibiotics postoperative because the surgeon considered the insertion had been difficult with an increased risk of infection.

In all the patients with cystic fibrosis there was an initial decrease in respiratory function but this started to improve after 24 hours as postoperative pain decreased. In all patients with cystic fibrosis respiratory function returned to preoperative levels.

Results

The 47 systems have now been implanted for between two and 104 weeks.

The effective life of the system is taken to last until elective removal or death of the child with the system still functioning. Most of the systems are still in use, but in non-functioning systems effective life extends until the date on which the system was last known to function satisfactorily. The range of the effective life is from 0 to 104 weeks (mean 31·8). In three patients with cancer we were never able to use the system for the purpose for which it was implanted. Five systems were used to give total parenteral nutrition.

Twenty systems are no longer in use. Ten children died with the system in place. In eight it was still functioning, and in three of these patients it was used for infusion of opiates for relief of pain during terminal care. In three patients with cancer the functioning systems were removed electively under general anaesthesia after completion of courses of chemotherapy. Seven systems were removed because of complications. No child died from a problem associated with the catheter.

Patients with cystic fibrosis showed overall general improvement in respiratory function during the months after implantation, and this may be associated with the improved quality of the courses of antibiotics given intravenously—that is, doses were not missed because of difficulties in gaining venous access.

COMPLICATIONS

Seven systems have been removed because of complications, the most common of which were blockage, haemorrhage, infection, and mechanical failure.

Blockage. There have been 14 blockages in 11 children. Unblocking was attempted 11 times with either urokinase or streptokinase, and was successful in eight. In one teenager with cystic fibrosis the system became blocked three times; on the third occasion urokinase failed to clear the block, and the entire system was replaced under sedation and local anaesthesia. The second system became blocked within a week, and there was strong evidence that the patient was abusing the system.

Haemorrhage. Four children, all thrombocytopenic, had bled locally postoperatively despite prophylactic transfusions of platelets. In two the haemorrhage was severe and in one child it was impossible, even with ultrasonography, to visualise the system under the haematoma. This child had the haematoma evacuated and had no more episodes of bleeding after further transfusions of platelets and fresh frozen plasma.

The other two children each had a moderate episode of bleeding, and in one it was controlled by infusion of fresh frozen plasma and vitamin K. The other child received no additional treatment, but her system was difficult to find because of the overlying haematoma.

Infection. Local infection of the skin occurred on six occasions in three patients, two with cancer and one with cystic fibrosis. Two of the patients with cancer also had systemic infections. One child had septicaemia caused by *Escherichia coli* at the time that a pustule appeared over the portal site; the infection resolved after treatment with ceftazidime, cloxacillin, and vancomycin given intravenously. The second child developed a skin pustule and septicaemia caused by *Staphylococcus aureus* that was resistant to prolonged antimicrobial treatment; the organism was grown in culture of the tip of the catheter after the system had been removed.

In a patient undergoing bone marrow transplantation the catheter blocked at the same time as *Staphylococcus epidermidis* was grown in cultures from both the line and the peripheral blood. No attempt was made to clear the infection and the system was removed immediately.

Two other patients developed erythema over the portal site that resolved after treatment with antibiotics given intravenously, although no organisms were grown from cultures of the blood.

One child with cystic fibrosis had three systems inserted. Her second system was removed because of the clinical suspicion of infection but this was not proved bacteriologically. She died while the third system was in place.

Mechanical problems. One child developed pain and redness over the portal site after injection of the solution of normal saline and heparin. The chest radiograph showed that the catheter tubing was lying free in the right atrium. The catheter was removed with a cardiac catheter that was inserted into the femoral vein under local anaesthesia. The rest of the system was later removed under general anaesthesia, and examination showed that the locking device was still in position over a short length of catheter that had fractured. This complication has been reported previously[4] [5] and the manufacturers have introduced a new locking device to reduce the possibility of it happening again. No patient has developed deep vein thrombosis of the arm, although this complication has been reported in adult patients.[6]

One patient dislodged the needle during the infusion of a solution for parenteral nutrition, some of which extravasated subcutaneously. The resulting erythema and swelling settled spontaneously.

In one patient with cystic fibrosis blood flowed back into the system during postural drainage on two occasions, but the system was flushed and the problem did not recur.

Discussion

The Port-A-Cath implantable venous access system has been a considerable advance in management in our paediatric unit. As our experience in the insertion, use, and care of these systems has increased we have encountered fewer problems. Because they are inserted in the subcutaneous tissue, the systems are comparatively tamper proof, which is useful for younger children. One child who previously had a long tunnelled line, pulled it out, and another child's tunnelled line fell out. Frequent or unexplained difficulties that occur when the systems are in use should, however, alert one to the possibility of abuse of the line.

The systems have been particularly useful in families in which social or language problems may have made daily flushing of a long tunnelled line difficult. Teenagers have expressed preference for the implantable systems; they are less conspicuous than long tunnelled lines, but should be carefully positioned as their contours may be an embarrassment. The systems do not interfere with swimming or other activities and there is no need for daily flushing. Infection of the systems has not been a particular problem, but strict asepsis in all procedures is essential.

The main benefits of implantable systems compared with long tunnelled lines are their low infection rate and the minimal care that is needed when they are not in use. The latter is a particular advantage when there are long intervals between use (such as in patients with cystic fibrosis in whom the need for good intravenous access will be lifelong but there may be intervals of several months between treatments).

Problems of bleeding should be anticipated in children with thrombocytopenia and disorders of clotting, and these should be corrected as far as possible before the operation. Insertion in patients with cystic fibrosis should be done with adequate antibiotic prophylaxis and physiotherapy if the detrimental effects of a general anaesthetic[7] are to be avoided. Local anaesthetic cream is useful in those children upset by the discomfort of putting a needle into the system.

Although the initial cost of a tunnelled line is less than that of an implanted system, the higher maintenance costs of the tunnelled line make it equally expensive after four months. We are continuing to place long tunnelled lines in children in whom bone marrow transplantation is a possibility in the future.

Despite requiring a needle to gain access to the portal the totally implantable systems are well tolerated by the children, accepted by their parents, and preferred by the nursing staff. The use of these systems is now well established in the management of our patients with cancer, and their use in patients with cystic fibrosis who require repeated courses of antibiotics intravenously is increasing.

We thank the paediatric surgeons who inserted the devices, particularly Mr RD Spicer; the Cystic Fibrosis Research Trust for funding Dr J Gilbert (the clinical research fellow in cystic fibrosis); and the Joseph Levy Charitable Foundation for funding Sister T Robinson (the cystic fibrosis liaison sister). We also thank Dr CC Bailey and Dr IJ Lewis for sharing their experience and permitting us to report their patients.

References

[1] Stockwell M, Adams M, Andrew M, Cameron G, Pai K. Central venous catheters for out-patient management of malignant disorders. *Arch Dis Child* 1983;**58**:633–5.
[2] Darbyshire PJ, Weightman NC, Speller DCE. Problems associated with indwelling central venous catheters. *Arch Dis Child* 1985;**60**:129–34.
[3] McDowell HP, Hart CA, Martin J. Implantable subcutaneous venous catheters. *Arch Dis Child* 1986;**61**:1037–8.
[4] Martin AJ, Morris LL, Reece J, Ford WDA, Cassey J, Goldblatt E. Totally implantable vascular access in treatment of cystic fibrosis. *Lancet* 1986;**ii**:293.
[5] Lokich JL, Bothe A, Benotti P, Moore C. Complications and management of implanted venous access catheters. *J Clin Oncol* 1985;**3**:710–7.
[6] Woll PJ, Rubens RD. Totally implantable vascular access for long term chemotherapy. *Br Med J* 1986;**292**:761.
[7] Price JF. The need to avoid general anaesthesia in cystic fibrosis. *J R Soc Med* 1986;**79**(suppl 12):10–2.

Correspondence to Dr J Gilbert, Regional Cystic Fibrosis Unit, St James's University Hospital, Beckett Street, Leeds LS9 7TF.

Accepted 5 August 1988

Archives of Disease in Childhood, 1989, **64**, 124–128

Symptoms and signs of progressive hydrocephalus

M KIRKPATRICK, H ENGLEMAN, AND R A MINNS

Department of Neurology, Royal Hospital for Sick Children, Edinburgh

SUMMARY The clinical features of 107 cases of children with hydrocephalus and measured raised intraventricular pressure were analysed retrospectively. Fifty one children had recently been diagnosed as having hydrocephalus, and the remainder had had shunts injected to direct the cerebrospinal fluid. The most common symptoms in the group were vomiting, behavioural changes, drowsiness, and headaches. The most common clinical signs were inappropriately increasing occipitofrontal head circumferences, tense anterior fontanelles, splayed sutures, and distension of the scalp veins. Half the infantile cases of hydrocephalus were without symptoms, and a quarter of the cases with cerebrospinal fluid shunts and measured raised intraventricular pressure were without signs. There were no fewer than 33 different clinical signs including several unusual ones, such as macular rash and sweating. We believe that the presentation of hydrocephalus with raised intraventricular pressure is sufficiently variable, unusual, or even absent to justify the direct measurement of intracranial pressure.

The classical adult presentation of raised intracranial pressure (headache, vomiting, and papilloedema[1]) is rare in children with progressive hydrocephalus. There are few studies of the clinical presentation of hydrocephalus with raised intracranial pressure either before or after an operation to divert the cerebrospinal fluid.

There are certainly no studies in which raised intracranial pressure has been confirmed by direct measurement, and such reports that do exist in children frequently include those with causes of raised intracranial pressure other than hydrocephalus alone. The aim of this study therefore was to document the symptoms and signs of 107 cases of progressive hydrocephalus (that is, hydrocephalus with raised intracranial pressure) in which the clinical features were documented and raised ventricular pressure had been confirmed on direct measurement.

Patients and methods

All the patients were admitted to the neurology unit at the Royal Hospital for Sick Children, Edinburgh, from 1975 onwards and they all had progressive hydrocephalus with or without a ventriculoperitoneal shunt in situ. Patients who had raised intracranial pressure from encephalopathies due to brain swelling or cerebrovascular congestion, or intracerebral space occupying lesions, were excluded (even if there was also hydrocephalus). Those with ventriculitis were also excluded. Table 1 shows the underlying aetiologies in the 107 cases. Hydrocephalus associated with spina bifida and idiopathic hydrocephalus were the most common presentation (65%).

Fifty one of the 107 cases had clinical features and a documented recording of raised intracranial pressure before any procedure to divert the cerebrospinal fluid was undertaken (32 boys and 19 girls). Fifty six cases presented with raised intracranial pressure and ventriculoperitoneal shunts in situ, the clinical features thus representing shunt malfunction (29 boys and 27 girls). Fifty one were infants (44 of the non-shunted and seven of the shunted), 22 cases were between the ages of 1 and 4 (two of the non-shunted and 20 of the shunted), and 34 cases were aged 5 or over (five of the non-shunted and 29 of the shunted).

Table 1 *Original aetiology of hydrocephalus*

Diagnosis	*No*
Hydrocephalus associated with spina bifida complex	58
Idiopathic	14
Post haemorrhagic hydrocephalus	14
Post meningitic hydrocephalus	11
Aqueduct stenosis	8
Hydranencephaly	1
Congenital toxoplasmosis	1

The data that were recorded included name, age, sex, the measured intracranial pressure, the duration of symptoms and signs before the raised intracranial pressure was diagnosed, the symptoms and signs themselves, and whether or not a cerebrospinal fluid shunt had already been injected. If hydrocephalus and raised intracranial pressure (in the absence of any other cause for raised pressure) were confirmed on admission, the pro forma was completed and the data were analysed retrospectively.

The method of measurement of intracranial pressure varied; for those who presented in infancy without a shunt, it was measured percutaneously through the anterior fontanelle or through a Rickham ventriculostomy reservoir that had been inserted as an elective procedure. For those patients with ventriculoperitoneal shunts in situ, the pressure was measured through separate ventriculostomy reservoirs. It has been our practice to insert a subcutaneous cerebrospinal fluid reservoir at the same time as the shunt, thus enabling us to measure the intracranial pressure directly whenever there was a suspicion of shunt malfunction.[2] In all cases a Gaeltec miniature strain gauge transducer was used and a direct recording of an opening pressure, maximum resting pressure, or mean overnight pressure was obtained.

Results

The most common presenting symptoms and signs of progressive hydrocephalus are shown in table 2. This group comprises both early hydrocephalus in non-shunted children and those with shunt malfunction.

The maximum sustained intracranial pressure measured in these cases was between 10 and 20 mm Hg in 12 (11%), between 20 and 29 mm Hg in 29 (27%), and over 30 mm Hg in 60% of cases. There was no correlation between any clinical feature and the measured intracranial pressure.

Fifty eight had symptoms and signs for less than two weeks before the diagnosis of raised intracranial pressure was made (54%). Twenty one (20%), however, had symptoms and signs for longer than one month and this group includes six cases who had symptoms and signs for more than three months before diagnosis.

The 51 cases of progressive hydrocephalus before surgical treatment have a different range of symptoms and signs from the total group (table 3). This group, as would be expected, contains many more younger children and half of these with measured raised intracranial pressure were asymptomatic.

The second subgroup (56 cases with shunt malfunction) is shown in table 4. They are older than the first subgroup, and their signs are even more varied with no obvious signs on clinical examination in a quarter.

Table 2 *Most common clinical features of progressive hydrocephalus, both shunted and non-shunted*

	No (%)
Symptoms:	
Vomiting	35 (33)
Behaviour change (including irritability)	32 (30)
Drowsiness or lethargy	30 (28)
Headache	30 (28)
Asymptomatic	30 (28)
Anorexia	15 (14)
Stiff neck or back ache	8 (7)
Signs:	
Inappropriately increasing occipitofrontal	43 (40)
circumference	33 (31)
Tense anterior fontanelle	22 (21)
Splayed cranial sutures	19 (17)
Scalp vein distension	16 (15)
Sunsetting or loss of upward gaze	15 (14)
No signs	14 (13)
Decreased conscious level	13 (12)
Neck retraction or rigidity	11 (10)
Acute strabismus	9 (8)
Pupillary changes	8 (7)
Papilloedema	8 (7)
Distended retinal veins	

Other less frequent symptoms were: jitteriness, sleep disturbance, sluggish valve, fits, abdominal pain, deteriorating school performance, pallor, and failure to thrive. *Other less frequent signs were:* tonic fits, pallor, sluggish valve, decerebration, optic atrophy, nystagmus, bradycardia, hypertension, profuse sweating, neurogenic stridor, macular rash, return of tonic neck reflex, hemiparesis, ataxia, sudden blindness, Cheyne-Stokes respiration, apnoeic or cyanotic episodes, cardiorespiratory arrest, ptosis, VII and XII cranial nerve palsies, and vasomotor changes.

Table 3 *Most common clinical features of progressive hydrocephalus in the non-shunted group (n=51)*

	No (%)
Symptoms:	
Asymptomatic	25 (49)
Headache or irritability	17 (33)
Vomiting	8 (16)
Signs:	
Inappropriately increasing occipitofrontal circumference	39 (76)
Tense anterior fontanelle	33 (65)
Splayed sutures	20 (39)
Scalp vein distension	17 (33)
Sunsetting or loss of upward gaze	11 (22)
Neck retraction or rigidity	7 (14)

Other symptoms (in 5%–10% of cases): jittery (infants), anorexia, drowsiness or lethargy, and stiff neck. *Other signs (in 5%–10% of cases):* decreased conscious level, pupillary changes, neurogenic stridor, decerebration, and papilloedema.

Table 4 *Most common clinical features of progressive hydrocephalus in the shunted group (n=56)*

	No (%)
Symptoms:	
Vomiting	27 (48)
Drowsiness or lethargy	26 (46)
Headache	26 (46)
Behaviour change (including irritability)	21 (38)
Anorexia	10 (18)
Signs:	
No clinical signs	14 (25
Decreased conscious level	10 (18
Acute strabismus	10 (18
Neck retraction	6 (11
Distended retinal veins	6 (11

Other symptoms (in 5%–10% of cases): valve not working, sleep disturbance, stiff neck, asymptomatic, and fits. Other signs (in 5%–10% of cases): sluggish valve, sunsetting, papilloedema, tonic fits, pallor, inappropriately increasing occipitofrontal circumference, tense anterior fontanelle, optic atrophy, bradycardia, profuse sweating, nystagmus, hypertension, and macular rash.

Discussion

There are two distinct groups of patients with progressive hydrocephalus in this study: those with and those without diverting shunts. Those with shunts and raised intracranial pressure, therefore, have clinical features representative of shunt malfunction, that is blockage or disconnection.

We were not concerned with arrested hydrocephalus, or with ventriculomegaly resulting from atrophic or ischaemic parenchymal damage as may be seen, for example, in preterm infants with periventricular cystic leukomalacia; they do not have raised intracranial pressure and therefore do not fulfil the entry criteria for this study. Nor were we concerned with other causes of raised intracranial pressure in children such as cerebral oedema or space occupying lesions (even if dilated ventricles were a symptom), as in those cases the clinical features may be a reflection of the disease itself. Tadros *et al* reported 100 adult cases of raised intracranial pressure that had the clinical features of headache, papilloedema, disturbance of consciousness, vomiting, optic atrophy, false localising signs, and fits (in decreasing order of frequency).[3] Most of these patients, however, had intracranial tumours.

MOST COMMON SYMPTOMS

Vomiting—is a non-specific symptom in childhood (and may therefore be a reason for late presentation or delay in diagnosis). It was the commonest presenting symptom in the shunted group (n=27) and the third most frequent presentation in the non-shunted group (n=8).

Behavioural change—including irritability—was the second most frequent symptom in the whole group (n=32). It seemed to be a frequent presentation of both subgroups and does not happen only in those with closed sutures, but at all ages. Irritability in infants may have reflected headaches but, like vomiting, is a non-specific symptom.

Headache—was more common in the older shunted group (n=26). The headache associated with raised intracranial pressure classically occurs after waking from a phase of rapid eye movement sleep when there is increased cerebral blood flow and a nocturnal rise in intracranial pressure.[4] In the series of intracranial tumours reported by Tadros *et al*, headaches were reported in all the patients.[3]

Anorexia—occurred in 15 cases (14%). This may, together with vomiting and a long duration of symptoms before diagnosis of raised intracranial pressure, have been the reason for the failure to thrive of one case in this series.

Many of the symptoms of raised pressure (vomiting, behavioural changes, drowsiness, headaches), are similar to symptoms of upper respiratory infection. The reasons for this may be firstly, that children with upper respiratory infection have increased cerebral blood flow and in a hydrocephalic child with abnormal cerebrospinal fluid dynamics this may result in a rise in intracranial pressure. Secondly, some cerebrospinal fluid may be absorbed through the paranasal sinuses[5] and therefore a rise in intracranial pressure may lead to facial congestion, headache, and so on—similar to an upper respiratory illness.

MOST COMMON CLINICAL SIGNS

Inappropriately increasing occipitofrontal circumference—was the most common sign in the non-shunted group and occurred in 39 (76%) of cases, all of whom were infants. This was a presenting sign, however, in only four cases (also infants) in the shunted group. Dandy in 1920 considered that all the symptoms and signs accompanying hydrocephalus were the direct result of pressure exerted by the cerebrospinal fluid.[6] Though an increasing head circumference is usually a direct effect of raised intracranial pressure, there may be a secondary effect of intracranial venous obstruction leading to an increased choroid plexus capillary pressure and a subsequent further rise in cerebrospinal fluid production.[7] Thus the expanding head circumference is compensatory and acts as a buffer.

A tense anterior fontanelle—was the second most common finding in the whole group (n=33, 65%). In conditions of raised intracranial pressure the normally concave and pulsatile fontanelle becomes tense, and at extremely high pressure loses its pulsatility.

Splayed sutures were the third most common clinical sign and were present in 20 cases in the non-shunted group and two (both infants) in the shunted group. The clinical features clearly depend on whether the raised intracranial pressure occurs in an expansile or non-expansile head. Sutural closure begins before birth with fusion of the metopic sutures and progresses through posterior and anterior fontanelle closure up to age of 12 years when it is thought that raised intracranial pressure can no longer separate the sutures.

Distended scalp veins—were present in a third of the cases in the non-shunted group. These are usually particularly prominent in the frontal and temporal regions. Spalteholz valves are situated between the intracranial and extracranial veins, and allow a unidirectional flow to the outside. Part of the cerebral blood flow is therefore drained by these and raised intracranial pressure is transmitted to them.

'Sunsetting'—(an inability to look upwards, found mostly in infants) may initially be intermittent but later becomes continuous, and is due to pressure on the superior quadrigeminal plate against the free edge of the tentorium. There is, however, a complex of signs resulting from lesions in this area known as the Koerber-Salus-Elschnig sylvian aqueduct syndrome.[8] This consists of paralysis of upward gaze, pupillary abnormalities, abnormalities of convergence and nystagmus. Sunsetting, pupillary changes, and nystagmus occurred in 30 (28%) of all cases.

Absence of symptoms—in the whole group there was an absence of symptoms despite the presence of clinical signs in 30 (28%). In the non-shunted group there were 25 patients who were symptom free (49%), all of whom were infants. Thus in infants without a shunt, progressive hydrocephalus was asymptomatic in almost half the cases, but by contrast only 7% of the shunted group were symptom free.

Absence of clinical signs in the presence of symptoms, however, occurred in 14% of the whole group and was the most frequent presentation in the shunted group (25%). We believe that this supports the case for the direct measurement of the intracranial pressure, because one cannot rely on clinical features to make the diagnosis.

Decreased conscious level—14 cases in the whole group had a decrease in conscious level (13%), four in the non-shunted and ten in the shunted group. It is generally assumed that coma is an infrequent presentation of hydrocephalus, but lesser degrees of impaired consciousness are not uncommon. Coma can occur with concomitant plateau waves on the intracranial pressure tracing, and may complete the clinical Charcot triad of pupillary dilatation and ipsilateral hemiplegia in the course of tentorial herniation as a complication of acute hydrocephalus.

UNUSUAL CLINICAL FEATURES

Neurogenic pulmonary oedema from a sudden rise in intracranial pressure was described by Ducker,[9] who found that he could reproduce it experimentally in animals in several different ways. The bobble head doll syndrome caused by dilatation or colloid cysts of the third ventricle consists of 2–3Hz oscillatory movements of the head and developmental delay.[10] No child in this series had either pulmonary oedema or the full syndrome.

Profuse sweating occurred with raised intracranial pressure in four cases in all. The original description of diencephalic autonomic epilepsy by Penfield in 1929[11] included profuse sweating as one of the features, but some authors have speculated that this was as a result of raised intracranial pressure.[12] We have documented some previously unreported signs—for example, a *macular rash* occurred in three cases on the extensor surfaces of the limbs at the same level of intracranial pressure on each occasion.

Ptosis is also an unusual presentation and *autonomic dysfunction* such as abdominal pain and pallor were more common than we expected.

Neurogenic stridor was present in four cases, all of whom were infants before shunting. This represents deranged lower brain stem function caused by bilateral cortico-bulbar disruption, and may occur alone or with other features of pseudobulbar palsy.[13] Stridor may also occur after acute ventricular decompression of cerebrospinal fluid with an accompanying upward cone. Other evidence of *pseudobulbar paresis* included sucking and feeding difficulties, although frequently hydrocephalic infants with seriously raised intracranial pressure will feed and suck well. Difficulties with phonation, drooling, regurgitation, and recurrent aspiration pneumonia may also result from brain stem dysfunction.

It is of interest that *papilloedema* occurred in only eight cases in the whole group (8%), two of whom were infants. In infantile hydrocephalus papilloedema occurs less often than stridor, pupillary changes, and diminished level of consciousness. This is in pronounced contrast to patients with infratentorial and supratentorial tumours among whom the incidence of papilloedema is 70% and 50%, respectively.[14]

CHRONIC SYMPTOMS

The chronic symptoms of presentation of hydrocephalus and raised intracranial pressure must be distinguished from the clinical features of arrested hydrocephalus. The latter include ataxic and spastic cerebral palsy,[15] hypothalamic and pituitary disturbance (for example, precocious puberty),[16–18] mental retardation, and specific learning disorders.[19] Although we encountered some patients with acute hemiplegia or ataxia, these signs all reverted to normal after relief of the raised intracranial pressure.[20]

Twenty per cent of cases had had features present for more than one month, and six cases for more than three months. The clinical features that we recognised in those with a long duration of presentation were an insidious deterioration in school performance, intermittent headaches over many months, behavioural changes; failure to thrive, and dizziness. Many of these features resolved after relief of cerebrospinal fluid pressure.

In conclusion, therefore, we have shown the variability, unreliability, unusual nature, and even absence of the clinical features of hydrocephalus with raised intracranial pressure. Because imaging is a static investigation, and does not invariably indicate the degree or even the presence of raised intracranial pressure, we feel that our results highlight the need for direct measurement of intracranial pressure as the only sure way to establish its presence. Any unexplained clinical features in children with a cerebrospinal fluid shunt should alert the physician to the possibility of raised pressure from shunt malfunction.

We thank Action Research for the Crippled Child for continued support of this research.

References

1 Bannister R, ed. *Brain's clinical neurology*. 6th ed. Oxford: Oxford University Press, 1985:229.

2 Leggatt JRS, Baxter P, Minns RA, *et al*. Role of a separate subcutaneous cerebrospinal fluid reservoir in the management of hydrocephalus. *Br J Neurosurg* 1988;**2**:327–38.

3 Tadros FW, Serour H, Zaki SA, Sakr R. The so-called general symptoms of increased intracranial pressure. *Postgrad Med J* 1962;**38**:417–6.

4 Cooper R, Hulme A. Intracranial pressure and related phenomena during sleep. *J Neurol Neurosurg Psychiatry* 1966;**29**: 564–77.

5 Weed LH, McKibben PS. Pressure changes in the cerebrospinal fluid following intravenous injections of solutions of various concentrations. *Am J Physiol* 1919;**48**:512–30.

6 Dandy WE. The diagnosis and treatment of hydrocephalus resulting from strictures of the aqueduct of Sylvius. *Surg Gynecol Obstet* 1920;**31**:340–58.

7 Anderweg J. *The cause of hydrocephalus*. Rotterdam: Bronder-Offset BV, 1976:266–8.

8 Chattha AS, DeLong GR. Sylvian aqueduct syndrome is a sign of acute obstructive hydrocephalus in children. *J Neurol Neurosurg Psychiatry* 1979;**38**:288–96.

9 Ducker TB. Increased intracranial pressure and pulmonary edema. 1. Clinical study of 11 patients. *J Neurosurg* 1968;**28**: 112–7.

10 Tomasovic JA, Nellhaus G, Moe PG. The bobble-head doll syndrome: an early sign of hydrocephalus. *Dev Med Child Neurol* 1975;**17**:777–83.

11 Penfield W. Diencephalic autonomic epilepsy. *Arch Neurol* 1929;**22**:358–74.

12 Summers DG, Young AC, Little RA, Stoner HB, Forbes WSTC, Jones RAC. Spontaneous periodic hypothermia with lipoma of corpus callosum. *J Neurol Neurosurg Psychiatry* 1981;**44**:1094–9.

13 Adeloye A, Singh SP, Odeku EL. Stridor, myelomeningocele and hydrocephalus in a child. *Arch Neurol* 1970;**23**:271–3.

14 Bell WE, McCormick WF. Symptoms, signs and physiologic concepts. In: *Increased intracranial pressure in children*. 2nd ed. Philadelphia: WB Saunders, 1978:7.

15 Hagberg B, Sjorgen I. The chronic brain syndrome of infantile hydrocephalus. *Am J Dis Child* 1966;**112**:189–96.

16 Kim CS, Bennett DR, Roberts TS. Primary amenorrhoea secondary to non communicating hydrocephalus. *Neurology* 1969;**19**:533–5.

17 Fiedler R, Krieger DT. Endocrine disturbances in patients with congenital aqueduct stenosis. *Acta Endocrinol* 1975;**80**:1–13.

18 Hier DB, Wiehl AC. Chronic hydrocephalus associated with short stature and growth hormone deficiency. *Ann Neurol* 1977;**2**:246–8.

19 Lonton AP. The relationship between intellectual skills and the computerised axial tomograms of children with spina bifida and hydrocephalus. *Z Kinderchir* 1979;**28**:368–74.

20 Bolthauser E, Hirsig J, Isler W, Rickham PP. Hemiparesis: an uncommon symptom of hydrocephalus or shunt dysfunction. *Z Kinderchir* 1980;**30**:191–7.

Correspondence and requests for reprints to Dr R A Minns, Department of Neurology, Royal Hospital for Sick Children, Edinburgh EH9 1LF.

Accepted 26 April 1988

Archives of Disease in Childhood, 1989, **64,** 129–134

Renal tubular proteinuria and microalbuminuria in diabetic patients

D M GIBB,* P A TOMLINSON,† N R DALTON,† C TURNER,† V SHAH,*
AND T M BARRATT*

*Department of *Paediatric Nephrology, Institute of Child Health, London, and †Department of Paediatrics, United Medical and Dental Schools of Guy's and St Thomas's Hospitals, London*

SUMMARY The urinary extraction of albumin, retinol binding protein, and N-acetyl-β-D-glucosaminidase were studied in 60 children with insulin dependent diabetes mellitus and in 45 normal children to find out whether the renal tubules played a part in causing the early increase in urinary excretion of albumin that occurs in diabetes mellitus. Two overnight urine samples were collected and the protein excretion measured and expressed as the geometric mean of the protein to creatinine ratio (urinary albumin:creatinine ratio, urinary retinol binding protein:creatinine ratio, and urinary N-acetyl-β-D-glucosaminidase:creatinine ratio, respectively). The excretion of all three proteins was significantly higher in the diabetic children with 15 (25%) of urinary albumin:creatinine ratio, 16 (27%) of urinary retinol binding protein:creatinine ratio, and 43 (72%) of urinary N-acetyl-β-D-glucosaminidase:creatinine ratio values being above the normal range. Significant correlations were observed between urinary albumin:creatinine ratio and urinary retinol binding protein:creatinine ratio, urinary albumin:creatinine ratio and urinary N-acetyl-β-D-glucosaminidase:creatinine ratio, and urinary retinol binding protein:creatinine ratio and urinary N-acetyl-β-D-glucosaminidase:creatinine ratio. There were also significant correlations between glycated haemoglobin 1c (HbA_{1c}) and these proteins, especially N-acetyl-β-D-glucosaminidase. No correlations were observed with the fractional excretion of sodium, flow rate of urine, glomerular filtration rate, or blood pressure.

These data show that tubular abnormalities are present early in the course of insulin dependent diabetes mellitus and suggest that the early increase in urinary excretion of albumin may be at least partly tubular in origin, and that glycaemic control may influence this aspect of proximal tubular function.

Raised urinary excretion of albumin has been reported in 10–20% of children with insulin dependent diabetes mellitus.[1–4] The importance of this remains unclear, however, and the finding of a high within individual variability of urinary excretion of albumin in both normal and diabetic children,[5] and a possible association with the degree of immediate metabolic control in the diabetics, increases the problems of understanding its pathogenesis.

The excessive excretion of protein that characterises overt diabetic nephropathy is generally thought to be caused by increased glomerular permeability to protein, and it has been assumed that the variably raised urinary excretion of albumin that occurs early in diabetes is caused by a milder degree of the same pathogenic mechanism.[6 7] The reasons for this assumption include the fact that glomerular filtration rate is raised early in the course of insulin dependent diabetes mellitus,[8 9] the fact that antihypertensive drugs decrease urinary excretion of albumin in both diabetics[10] and patients with essential hypertension,[11] and the morphological alterations in the structure and biochemistry of the diabetic glomerular basement membrane early in the course of the disease.[12 13]

This interpretation of the early rise in the urinary excretion of albumin depends on the assumption that tubular fractional reabsorption of filtered albumin is unchanged. The presence of low molecular weight proteinuria undermines that assumption because it is caused by tubular dysfunction that might also impair the reabsorption of albumin.[14]

Urinary β_2 microglobulin is the principal low molecular weight protein that has been investigated in diabetic nephropathy. Results have been conflicting but the general conclusions were that although there may be an acute increase in β_2 microglobin excretion in poorly controlled diabetes, tubular impairment is important only in more advanced disease.[15–18]

Raised urinary excretion of retinol binding protein and N-acetyl-β-D-glucosaminidase have been noted in association with damage to the renal tubules.[19] Urinary excretion of retinol binding protein (a low molecular weight protein) correlates with that of β_2 microglobin in renal disease,[20] and recently was found to be raised in 15% of diabetic adults even without microalbuminuria.[21] N-acetyl-β-D-glucosaminidase (a lysosomal enzyme originating from the proximal renal tubule cell) is not filtered by the glomerulus, but is liberated into the tubular lumen with proximal tubular damage. Increased levels in the urine have been reported in diabetic children both with and without evidence of nephropathy.[22]

The aims of this study were firstly to investigate the urinary excretion of albumin, retinol binding protein, N-acetyl-β-D-glucosaminidase, and β_2 microglobin, and the associations among these proteins in the urine of normal and diabetic children, and secondly to investigate the association between glomerular haemodynamics and the excretion of these proteins. Thirdly we examined the associations between urinary excretion of these proteins and other measurements of tubular function and metabolic control.

Patients and methods

Sixty children and adolescents attending the diabetic clinics at the Hospital for Sick Children were investigated. Their mean age was 13·1 years (range 4·5–19) and the mean duration of their diabetes was seven years (range six months to 16½ years); 16 of the children were prepubertal, 17 in early puberty, and 27 in late puberty; there were 27 boys and 33 girls. None had evidence of urinary infection at the time of study. Concentrations of proteins in the urine were measured in all children as was the blood pressure; measurement of glomerular filtration rate was carried out in 44.

Excretion of proteins in the urine was investigated in 45 normal children, mean age 13·3 years (range 4·8–17). Control subjects for the studies of glomerular filtration rate comprised 15 normal adolescents and young adults with a mean age of 24·9 years (range 17–33) recruited from hospital staff and friends. The study was approved by the ethical committee of the Hospital for Sick Children.

Concentrations of albumin in the urine were measured by radioimmunoassay using a commercially available kit (Diagnostic Products Corporation); concentrations of retinol binding protein in the urine by an enzyme linked immunosorbent assay (ELISA) using rabbit antisera (Dako Ltd);[23] and the activity of N-acetyl-β-D-glucosaminidase in the urine by an automated colourimetric method using p-Nitrophenyl-N-acetyl-β-D-glucosamide (Sigma Chemical Co) as substrate.[24] Urinary creatinine was measured by the Jaffe reaction. Excretion of protein in the urine was expressed as the geometric mean of the ratio of the protein concentration to that of creatinine in two consecutive overnight urine samples (urinary albumin:creatinine ratio in mg/mmol; urinary retinol binding protein:creatinine ratio in μg/mmol; and urinary N-acetyl-β-D-glucosaminidase:creatinine ratio in μmol of p-nitrophenylic acid/hour/mmol). β_2 microglobin was measured by an ELISA in single random morning urine specimens collected during water diuresis placed immediately in sodium bicarbonate, and then frozen at −20°C. Results were also expressed as a concentration ratio with respect to creatinine (urinary β_2 microglobulin:creatinine ratio, in μg/mmol), and these are given only for the diabetic children.

Glomerular filtration rate was measured during a constant infusion of ^{51}chromium edetic acid under conditions of water diuresis with spontaneous voiding of urine.[25] Estimates of glomerular filtration rate were rejected if one or more individual clearances differed from the mean by more than 15%. Acceptable estimates of glomerular filtration rate were obtained in 41 of the 44 children studied.

Blood pressure was measured using a random zero sphigmomanometer with the child seated. Results were expressed as standard deviation scores standardised against the 1987 Task Force data for blood pressure in normal children.[26]

Urinary sodium and plasma sodium concentrations were measured by flame photometry. Fractional excretion of sodium measured in the diabetic children was calculated from the formula: fractional excretion of sodium=(urinary sodium/plasma sodium concentration)/(urinary creatinine/plasma creatinine concentration). In addition, as plasma sodium and creatinine concentrations were not measured in the normal children, the urinary excretion rates of sodium were compared in normal and diabetic children (mmol/minute).

Glycated haemoglobin 1c (HbA_{1c}) was measured by electrophoresis, the normal range being 5–8%.

Computation and statistical analysis were done using the Statistical Analysis System (SAS Institute Inc). Urinary albumin:creatinine ratio, urinary retinol binding protein:creatinine ratio, urinary N-acetyl-β-D-glucosaminidase:creatinine ratio and urinary β_2 microglobulin:creatinine ratio were shown to be logarithmically normally distributed by normal order plots.[5] Results were therefore transformed logarithmically before analysis. The unpaired Student's *t* test, linear regression by the least square method, and multiple regression, were used to analyse the data.

Results

Geometric means (range, 2 SD) for urinary albumin:creatinine ratio, urinary retinol binding protein:creatinine ratios, and urinary N-acetyl-β-D-glucosaminidase:creatinine ratios were significantly higher in diabetic compared with normal children (table 1). In the diabetic children, 15 (25%) of urinary albumin:creatinine ratio, 16 (27%) of urinary retinol binding protein:creatinine ratio, and 43 (72%) of urinary N-acetyl-β-D-glucosaminidase: creatinine ratio values were more than two standard deviations above the mean for the normal children.

Mean (SD) glomerular filtration rate in the diabetic children was 129 (19) ml/minute/1·73 m^2 surface area, which was significantly greater than 109 (13) (p<0·001) in the control subjects (table 2), and (30%) had values about the normal range. The mean diastolic (but not systolic) blood pressure standard deviation score was significantly raised in the diabetic children, as was the urinary flow rate but not the sodium excretion (table 2).

Significant positive correlations were found between urinary albumin:creatinine ratio and urinary retinol binding creatinine:creatinine ratio (r=0·67, p<0·0001), urinary albumin:creatinine ratio and urinary N-acetyl-β-D-glucosaminidase:creatinine ratio (r=0·55, p<0·0001) and urinary retinol binding creatinine:creatinine ratio and urinary N-acetyl-β-D-glucosaminidase:creatinine ratio (r=0·70, p<0·0001) (figs 1, 2, and 3). In 39 of the random

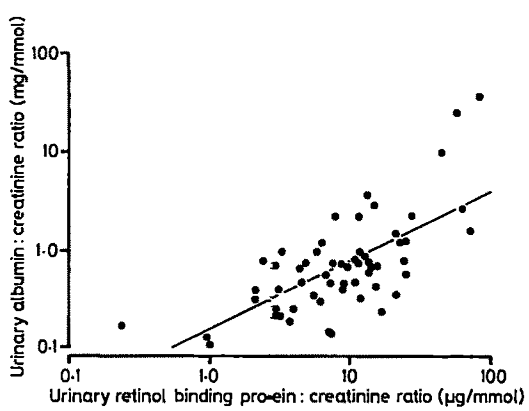


Fig 1 *Scattergram of urinary albumin:creatinine ratio and urinary retinol binding protein:creatinine ratio (data transformed logarithmically) Correlation coefficient is 0·67 (p<0·0001).*

Table 1 *Geometric means (ranges—2 SD) for measurements of protein excretion in children with insulin dependent diabetes mellitus and normal children*

	Diabetic children (n=60)	*Normal children (n=45)*	*p Value*
Urinary albumin:creatinine ratio (mg/mmol)	0·72 (0·08–6·9)	[illegible]·41 (0·14–1·17)	<0·001
Urinary retinol binding protein:creatinine ratio (µg/mmol)	8·5 (1·0–74·0)	5·8 (1·0–15·1)	<0·001
N-acetyl-β-D-glucosaminidase:creatinine ratio (µmol p-nitrophenylic acid/hour mmol)	39·8 (5·5–238)	5·8 (1·8–25·0)	<0·001

Table 2 *Mean (SD) urine flow rate, fractional excretion of sodium, sodium excretion rate, blood pressure standard deviation scores, glomerular filtration rate in children with insulin dependent diabetes mellitus and normal children*

	Diabetic children (n=60)	*Normal children (n=45)*	*p Value*
Urinary flow (ml/minute)	0·77 (0·44)	0·41 (0·23)	<0·001
Fractional excretion of sodium (%)	0·53 (0·35)	Not measured	
Sodium excretion rate (mmol/minute)	0·06 (0·04)	0·05 (0·03)	NS
Systolic blood pressure standard deviation score	+0·15 (0·65)	Not measured	NS‡
Diastolic blood pressure standard deviation score	+0·51 (0·82)	Not measured	<0·01‡
Glomerular filtration rate (ml/minute/1·73 m^2 surface area)	129 (19)*	109 (13)†	<0·001

*n=41; †n=15; ‡compared with the 1987 Task Force data for blood pressure in normal children.[26]

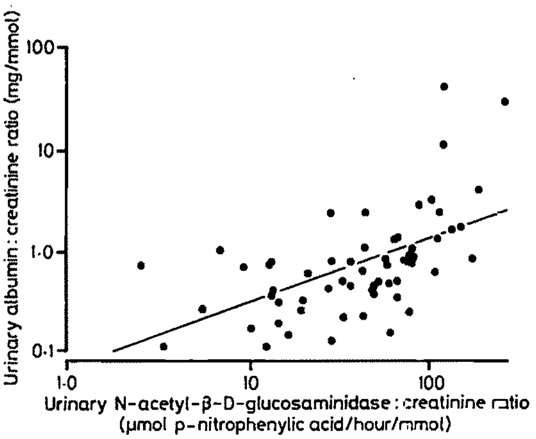


Fig 2 *Scattergram of urinary albumin:creatinine ratio and urinary N-acetyl-β-D-glucosaminidase:creatinine ratio (data transformed logarithmically). Correlation coefficient is 0·55 (p<0·0001).*

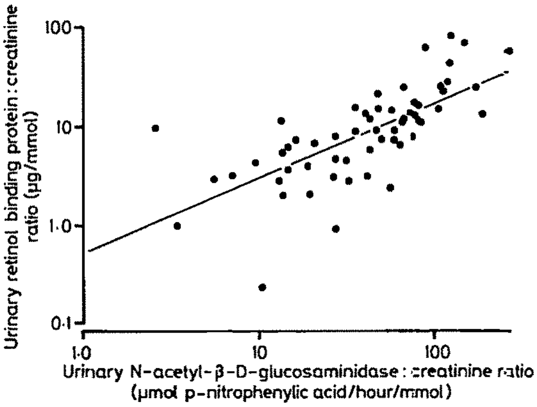


Fig 3 *Scattergram of urinary retinol binding protein:creatinine ratio and urinary N-acetyl-β-D-glucosaminidase: creatinine ratio (data transformed logarithmically). Correlation coefficient is 0·70 (p<0·0001).*

urine samples from the diabetic children, the pH was between 6·5 and 9·5. In these samples, the correlation between urinary β_2 microglobulin: creatinine ratio and urinary retinol binding protein: creatinine ratio was highly significant ($r=0{\cdot}68$, $p<0{\cdot}0001$).

Concentrations of all three proteins correlated weakly but significantly with age in diabetic but not in normal children, and there was a weak correlation between duration of disease and urinary N-acetyl-β-D-glucosaminidase:creatinine ratio but not with the other proteins (table 3). In the diabetic children, HbA_{1c} concentrations correlated with all three proteins (table 3). As age correlated with both HbA_{1c} concentration and excretion of the proteins, this was held constant by multiple regression analysis; the association between protein excretion and HbA_{1c} concentration remained significant for all three proteins.

When the association between urinary albumin: creatinine ratio and glomerular filtration rate was studied it was found that although there was no significant correlation between them ($r=0{\cdot}29$, NS), seven of 10 diabetic children who had urinary albumin:creatinine ratio above the the normal range also had glomerular filtration rate above the normal range ($p<0{\cdot}001$, χ^2). There was no association between urinary retinol binding protein:creatinine ratio or urinary N-acetyl-β-D-glucosaminidase: creatinine ratio and glomerular filtration rate, or between blood pressure and urinary excretion of any of the proteins. There was no correlation between urinary excretion of proteins and urinary flow rate or fractional excretion of sodium in either the diabetic or the normal children.

Discussion

We have found that children and adolescents with insulin dependent diabetes mellitus have significantly raised urinary excretion of albumin, retinol binding protein, and N-acetyl-β-D-glucosaminidase. The good correlation between the excretion of all three

Table 3 *Correlation coefficients for relationships between urinary albumin:creatinine ratio, urinary retinol binding protein:creatinine ratio, urinary N-acetyl-β-D-glucosaminidase:creatinine ratio and age, duration of disease and mean HbA_{1c} concentration*

	Urinary albumin:creatinine ratio	*Urinary retinol binding protein:creatinine ratio*	*Urinary N-acetyl-β-D-glucosaminidase: creatinine ratio*
Mean age	0·35*	0·35*	0·50***
Mean duration of disease	0·08	0·27	0·39**
Mean HbA_{1c} concentration	0·34*	0·36*	0·57***

*p<0·01, **p<0·001, ***p<0·0001.

proteins in the diabetic children suggests that the increased urinary excretion of albumin may, at least in part, be caused by proximal tubular dysfunction.

The main evidence that the early increase in urinary excretion of albumin in diabetes is of glomerular origin is that it is not paralleled by an increase in tubular proteinuria, particularly β_2 microglobin.[7] Several studies in adults with insulin dependent diabetes mellitus have shown normal 24 hour urinary excretion of this protein[15–18] and reported abnormalities have usually been associated with ketoacidosis,[27] poor metabolic control,[28] or exercise.[29] One reason for these conflicting results is likely to be the instability of β_2 microglobin in acid or extremely alkaline urine, and in the presence of pyuria, making it an unsuitable marker for assessing tubular dysfunction unless the patient is given an oral alkali before and during the period of urine collection.[30] An alternative method (which we undertook in this study) is to collect urine samples during water diuresis and immediately place them in sodium bicarbonate. We confirmed the results of Bernard *et al*,[20] who also found a good correlation between excretion of β_2 microglobin and retinol binding protein in random samples of urine from diabetic children.

Few other low molecular weight proteins have been investigated in diabetes. Raised concentrations of retinol binding protein have been reported in diabetic adults,[21] and Walton *et al* recently found raised urinary excretion of α1 microglobulin and κ light chains in diabetic children, and good correlations between them.[31] Contrary to our findings, they found no increase in urinary excretion of albumin in diabetic compared with normal children. However, although the amounts of albumin in the urine which they found in the diabetic children were similar to ours, the amounts in their normal children were higher than those found by most investigators (including ourselves).[1 25] In addition, the mean age of and duration of disease in the diabetic children that they studied were significantly lower than ours.

The correlation between the concentration of HbA_{1c} and excretion of the three proteins raises the possibility that poor glycaemic control may be important. The good correlation reported by Watanabe *et al*[22] between N-acetyl-β-D-glucosaminidase activity and urinary glucose concentration would support the experimental evidence that secretion of the enzyme by cultured fibroblasts correlates with the amount of glucose metabolised by the cells.[32] Glycosuria has been associated with alterations in tubular transport of sodium, calcium, and phosphate,[33] and could alter the transport of low molecular weight proteins such as retinol binding protein. Furthermore, competition has recently been reported between uptake of albumin and β_2 microglobin in rats, suggesting that tubular reabsorption of small and large molecules may not take place through distinct pathways as is currently thought.[34]

Although the flow rate of urine was increased in the diabetic children, we found no correlation with urinary excretion of protein. This is in accordance with the experimental work that has shown that reabsorption of phosphate, which is also decreased in diabetes,[35] is linked to absorption of glucose directly and is not a non-specific osmotic intraluminal effect. No change in reabsorption of phosphate is observed if mannitol is substituted for glucose.[35]

We found no correlations between excretion of the proteins and fractional excretion of sodium or the excretion rate of sodium; this was also reported by Ditzel *et al.*[33] We also found no correlations between glomerular filtration rate or blood pressure, or excretion of either retinol binding protein or N-acetyl-β-D-glucosaminidase. Although no linear correlation was found, however, a threshold association does exist between urinary albumin:creatinine ratio and glomerular filtration rate, as we have reported previously.[25]

In conclusion, our data demonstrating increased excretion of retinol binding protein and N-acetyl-β-D-glucosaminidase in association with positive correlations with urinary albumin:creatinine ratio in children with insulin dependent diabetes mellitus indicate that renal tubular function is impaired early in the course of the disease, and may be at least partly the cause of the early abnormal urinary excretion of albumin. Whether the tubular abnormalities are purely functional requires further study of the mechanisms of tubular absorption in both normal and diabetic subjects.

We thank Dr D Grant and Dr M Savage for permitting the diabetic children at the Hospital for Sick Children to take part in the study, Professor M Preece for permission to obtain urine samples from the children of Holywood School, Chard, Somerset, Ms J Jones and Dr D Dunger for help with collecting urine samples, and Mr W Wilson for measuring urinary creatinine concentrations and for his help with measuring glomerular filtration rates.

This project was supported by grants from Boehringer Ingelheim, the Kidney Research Aid Fund, and the Children Nationwide Medical Research Fund.

References

[1] Davies AG, Price DA, Postlethwaite RJ, Addison GM, Burn JL, Fielding BA. Renal function in diabetes mellitus. *Arch Dis Child* 1985;**60**:299–304.

[2] Mathiesen ER, Saurbrey N, Hommel E, Parving H-H. Prevalence of microalbuminuria in children with insulin-dependent diabetes. *Acta Endocrinol* 1986;**112**(suppl 275):14–22.

[3] Ellis D, Becker DJ, Daneman D, Lobes L, Drash AL. Proteinuria in children with insulin-dependent diabetes: rela-

tionship to duration of disease, metabolic control, and retinal changes. *J Pediatr* 1983;**102**:673–80.

[4] Mogensen CE. Urinary albumin excretion in early and longterm juvenile diabetes. *Scand J Clin Lab Invest* 1971;**28**:183–93.

[5] Gibb DM, Preece M, Shah V, Wilson W, Barratt TM. Variability of urine albumin excretion in normal and diabetic children. *Paediatric Nephrology* (in press).

[6] Mogensen CE. Microalbuminuria as a predictor of clinical diabetic nephropathy. 1987;**31**:673–89.

[7] Viberti GC, Keen H. The patterns of proteinuria in diabetes mellitus. *Diabetes* 1984;**33**:686–92.

[8] Brochner-Mortensen J, Ditzel J, Mogensen CE, Rodbro P. Microvascular permeability to albumin and glomerular filtration rate in diabetic and normal children. *Diabetologia* 1979;**16**: 307–11.

[9] Berg UB, Thalme B. Early renal functional changes in children with insulin-dependent diabetes mellitus—their relation to metabolic control. *Int J Pediatr Nephrol* 1984;**5**:15–21.

[10] Parving H-H, Smidt UM. Hypotensive therapy reduces microvascular albumin leakage in insulin-dependent diabetic patients with nephropathy. *Diabetic Medicine* 1986;**3**:312–5.

[11] Christensen CK. Rapidly reversible albumin and beta-2-microglobulin hyperexcretion in recent severe essential hypertension. *J Hypertens* 1983;**1**:45–51.

[12] Williamson JR, Kilo C. Basement membrane thickening and diabetic microangiopathy. *Diabetes* 1976;**25**:925–7.

[13] Beisswenger PJ. Glomerular basement membrane: biosynthesis and chemical composition in the streptozotocin diabetic rat. *J Clin Invest* 1976;**58**:844–52.

[14] Abrass CK. Diabetic proteinuria: glomerular or tubular in origin? *Am J Nephrol* 1984;**4**:337–46.

[15] Viberti GC, Mackintosh D, Bilous RW, *et al.* Proteinuria in diabetes mellitus: role of spontaneous and experimental variation of glycaemia. *Kidney Int* 1982;**21**:714–20.

[16] Mogensen CE. Renal function changes in diabetes. *Diabetes* 1976;**25**:872–9.

[17] Mathiesen ER, Oxenboll B, Johansen K, *et al.* Incipient nephropathy in type 1 (insulin-dependent) diabetes. *Diabetologia* 1984;**26**:406–10.

[18] Deckert T, Feldt-Rasmussen B, Djurup R, Deckert M. Glomerular size and charge selectivity in insulin-dependent diabetes mellitus. *Kidney Int* 1988;**33**:100–6.

[19] Kunin CM, Chesney RW, Craig WA, England AC, DeAngelis C. Enzymuria as a marker of renal injury and disease: studies of N-acetyl-β-glucosaminidase in the general population and in patients with renal disease. *Pediatrics* 1978;**62**:751.

[20] Bernard AM, Moreau D, Lauwerys R. Comparison of retinol-binding protein and β_2-microglobulin determination in urine for the early detection of tubular proteinuria. *Clin Chim Acta* 1982;**126**:1–7.

[21] Rowe DJF, Anthony F, Polak A, Shaw K, Ward CD. Retinol binding protein as a small molecular weight marker of renal tubular function in diabetes mellitus. *Ann Clin Biochem* 1987;**24**:477–82.

[22] Watanabe Y, Nunoi K, Maki Y, Nakamura Y, Fujishima M. Contribution of glycaemic control to the levels of N-acetyl-β-D-glucosaminidase and serum NAG in type 1 (insulin-dependent) diabetes mellitus without macroalbuminuria. *Clin Nephrol* 1987;**28**:227–31.

[23] Topping MD, Forster HW, Dolman C, Luczynska CM, Bernard AM. Measurement of urinary retinol-binding protein by enzyme-linked immunosorbent assay and its application to the detection of tubular proteinuria. *Clin Chem* 1986;**32**:1863–6.

[24] Marulin D. Rapid colorimetric assay of B-D-galactosidase and N-acetyl-β-D-glucosaminidase in human urine. *Clin Chim Acta* 1976;**73**:453–61.

[25] Gibb DM, Dunger DB, Levin M, Shah V, Smith C, Barratt TM. Early markers of the renal complications of insulin-dependent diabetes mellitus in children. *Arch Dis Child* (in press).

[26] National Heart, Lung and Blood Institute, Bethesda, Maryland. Report of the second task force on blood pressure control in children, 1987. *Pediatrics* 1987;**79**:1–25.

[27] Miltenyi M, Korner A, Tulassay T, Szabo A. Tubular dysfunction in type 1 diabetes mellitus. *Arch Dis Child* 1985;**60**:929–31.

[28] Parving H-H, Noer I, Deckert T, *et al.* The effect of metabolic regulation on microvascular permeability to small and large molecules in short-term juvenile diabetes. *Diabetologia* 1976; **12**:161–6.

[29] Mogensen CE. Renal function changes in diabetes. *Diabetes* 1976;**25**:872–9.

[30] Schardijn GHC, Statius van Eps LW. β_2-microglobulin: its significance in the evaluation of renal function. *Kidney Int* 1987;**32**:635–41.

[31] Walton C, Bodansky HJ, Wales JK, Forbes MA, Cooper EH. Tubular dysfunction and microalbuminuria in insulin dependent diabetes. *Arch Dis Child* 1988;**63**:244–9.

[32] Hultberg B, Isaksson A, Kjellström T. The effects of glucose and insulin on beta-hexosaminidase in cultured fibroblasts in diabetic and non-diabetic subjects. *Ann Clin Biochem* 1985;**22**: 133–6.

[33] Ditzel J, Brochner-Mortensen, J, Kawahara R. Dysfunction of tubular phosphate reabsorption related to glomerular filtration and blood glucose control in diabetic children. *Diabetologia* 1982;**23**:406–10.

[34] Bernard A, Viau C, Ouled A, Lauwerys R. Competition between low- and high-molecular-weight proteins for renal tubular uptake. *Nephron* 1987;**45**:115–8.

[35] Fox M, Thur S, Rosenberg L, Segal S. Impaired renal tubular renal function induced by sugar infusion in man. *J Clin Endocrinol Metab* 1964;**24**:1318–27.

Correspondence to Dr D Gibb, Department of Paediatric Nephrology, Institute of Child Health, 30 Guilford Street, London WC1N 1EH.

Accepted 30 June 1988

Archives of Disease in Childhood, 1989, **64,** 135–137

Seronegativity and HIV infection

P LEPAGE,* J BATUNGWANAYO,† AND P VAN DE PERRE‡

**Department of Paediatrics, Centre Hospitalier de Kigali, †Department of Respiratory Diseases, Centre Hospitalier de Kigali, and ‡AIDS Project, Kigali, Rwanda*

SUMMARY An African girl born to an HIV seropositive mother was seropositive during the neonatal period, became seronegative, and was again found to be seropositive at 18 and 20 months of age. We suggest that seronegative children born to seropositive mothers should be followed up for months or even years before HIV infection can be ruled out.

The diagnosis of human immunodeficiency virus (HIV) infection is usually confirmed by the detection of antibodies against HIV in serum. In children less than 15 months old born to HIV seropositive mothers, the presence of specific clinical signs and immunological abnormalities are needed in addition to the presence of HIV antibodies, to exclude a passive mother to child transfer of antibodies during pregnancy.[1] Among the serological tests, the enzyme linked immunosorbent assay (ELISA) is the commonest test used throughout the world because of its satisfactory sensitivity and specificity, its feasibility, and its low price. Nevertheless, HIV infected adults and children with negative ELISAs, and sometimes with negative confirmation tests such as western blot and indirect immunofluorescence as well, have been reported.[2-5]

We describe a girl born to an HIV seropositive mother who was seropositive during the neonatal period, became seronegative, and was found to be seropositive again at 18 and 20 months of age.

Methods

HIV antibodies were detected by a commercial ELISA (Vironostika, Organon Teknika) and by a commercial indirect immunofluorescent assay (IFA, JLC Allaman). In addition, all serum samples were tested by a western blot technique to search for IgG and IgM antibodies to HIV (Biotech Du Pont de Nemours). This latter test was performed after absorption of rheumatoid factor (RF absorbent, Behring). HIV antigen was tested using a commercial ELISA (Innogenetics), and serum immunoglobulins were quantitated by radial immunodiffusion (Nor-Partigen, Behring).

Case report

This girl has been followed up clinically (at least every month) and serologically since birth because her mother presented with persistent generalised lymphadenopathy and was diagnosed as HIV seropositive by ELISA and western blot (positive for all bands) during pregnancy.

The infant was born at full term, but was small for gestational age (birth weight 2300 g). She was 24 months old at the time of writing and had only had common minor infections such as acute diarrhoea and upper respiratory tract infections. Although she

Table *Sequential detection of HIV antibodies and HIV antigen and quantitation of serum immunoglobulins in a Rwandese child from birth to 20 months of age*

Age	*ELISA*	*Indirect immunofluorescent assay*	*IgG (western blot)*	*IgM (western blot)*	*HIV antigen*	*IgG (g/l)*	*IgA (g/l)*	*IgM (g/l)*
15 days	Positive	Positive	Positive	Negative	Negative	10·2	0·42	1·38
7 months	Negative	Negative	Weak positive	Negative	Negative	16·9	1·01	2·99
12 months	Negative	Negative	Negative (p24 only)	Negative	Negative	28·1	0·72	2·71
18 months	Positive	Positive	Positive	Negative	Negative	27·3	0·93	2·70
20 months	Positive	Positive	Positive	Negative	Negative	33·2	13·50	2·90

All values except IgG and IgA at 15 days old are above the upper limit of normal.

was growing steadily, her weight was only 8200 g and her height 78 cm at 24 months of age. Her clinical examination remained completely normal; she never showed any signs of persistent generalised lymphadenopathy, parotitis, or chronic otitis media. Her psychomotor development followed normal milestones. The chest radiograph was normal at 12 and 24 months of age. She was breastfed for 17 months. Except for routine immunisation, she never received any injections.

Five serum samples were available for immunological and serological analysis (table). The serum sample from 15 days after birth was positive for HIV antibodies by ELISA, indirect immunofluorescence and western blot (table). Two subsequent samples at 7 and 12 months were negative by ELISA and indirect immunofluorescence, and showed a reduction in reactivity on western blot (figure). The two latter samples (at 18 and 20 months) were reactive again by ELISA, indirect immunofluorescence, and western blot. At 15 days of life, IgM subclass hyperimmunoglobulinaemia was noted. After the 7 month sample the hyperimmunoglobulinaemia was also present for IgG and IgA.

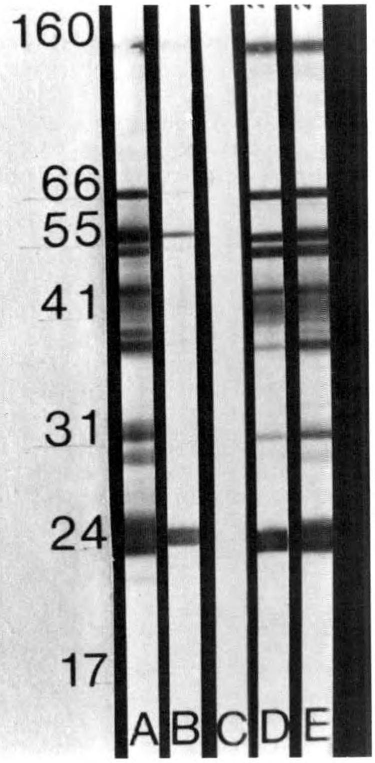


Figure *HIV IgG western blot pattern in sequential serum samples from a child born to a mother infected with HIV. Lane A=serum sample collected at 15 days of life; lane B=serum sample collected at 7 months; lane C=serum sample collected at 12 months; lane D=serum sample collected at 18 months; and lane E=serum sample collected at 20 months. Molecular weights expressed as kilodaltons.*

Discussion

The progressive loss of antibodies to HIV in a child in good general health is usually considered to be a good prognostic factor—that is, it indicates that the infant had acquired antibodies passively from his mother and was not infected perinatally.[1] The case presented here, as well as three others briefly described from Italy,[6] show that some infected children after being seropositive in the neonatal period may present for rather a long period without detectable antibodies in their serum. The occurrence of seronegative but virus positive subjects has been acknowledged among both adults and children.[2–5]

A child with epidemiological, clinical, and immunological evidence of AIDS, but without HIV antibodies from 8 months until her death at 14 months of age, has been described.[5] Nevertheless serum samples from the same child, when evaluated with more sensitive reagents, were found to be strongly positive for IgG antibodies to HIV.[7] Borkowsky *et al*[3] reported nine of 85 HIV infected children, six of whom were tested only once, who lacked HIV antibodies when measured by a commercial ELISA. Only four of these nine cases negative on ELISA had detectable antibodies on western blot analysis, or on ELISA with recombinant HIV antigens or both. All nine children had detectable levels of HIV antigen.[3] In the case reported here HIV antigen was never detected. This is not surprising because the antigen is only sporadically detected in the early stages of HIV infection in infants, and because of the comparative rarity of HIV antigen recovery by ELISA in HIV infected patients from Africa.[8] In some series[2 4] (but not all,[3 5] including our case), negative HIV antibodies seemed to be associated with hypogammaglobulinaemia. In contrast, in our case, severe hypergammaglobulinaemia was noticed when the child was 7 months of age, that is when she was seronegative. Thus hypergammaglobulinaemia in children less than 15 months old born to seropositive women could be an early immunological sign of HIV infection.

It is most likely that this child was infected transplacentally or during delivery, but she may have acquired the HIV infection postnatally. Indeed, HIV has been isolated from human milk,[9] and postnatal transmission through breast milk has been strongly suggested in four recent cases.[10–12] Postnatal infection could explain the delayed appearance of HIV antibodies in our patient.

Large prospective studies are needed to show what proportion of children born to HIV infected mothers become temporarily seronegative. Seronegative children born to seropositive mothers should be followed up for months or years before HIV infection can be completely ruled out, even if their clinical examination and psychmotor development remains normal. In addition, serum samples from these seronegative children should be tested by more sensitive assays than commercial ELISA, indirect immunofluorescence, and western blot.

References

[1] Centers for Disease Control. Classification system of human immunodeficiency virus (HIV) infection in children under 13 years of age. *MMWR* 1987;**36**:225–30.

[2] Pahwa S, Kaplan M, Fikrig S, *et al.* Spectrum of human T-cell lymphotropic virus type III infection in children: recognition of symptomatic, asymptomatic, and seronegative patients. *JAMA* 1986;**255**:2299–305.

[3] Borkowsky W, Krasinski K, Paul D, Moore T, Bebenroth D, Chandwani S. Human immunodeficiency virus infections in infants negative for anti-HIV by enzyme-linked immunoassay. *Lancet* 1987;**i**:1168–71.

[4] Español T, Garcia-Armui R, Boffil A, Sune J, Bertran JM. Hypogammaglobulinaemia and negative anti-HIV antibodies in AIDS. *Arch Dis Child* 1987;**62**:853–4.

[5] Marshall GS, Barbour SD, Plotkin SA. AIDS without antibody to HIV. *Lancet* 1987;**i**:446–7.

[6] Aiuti F, Luzi G, Mezzaroma I, Scano G, Papetti C. Delayed appearance of HIV infection in children. *Lancet* 1987;**ii**:858.

[7] Pyu KH, Ochs HD, Wedgwood RJ, Marshall GS, Barbour SD, Plotkin SA. Seronegativity and paediatric AIDS. *Lancet* 1987;**i**: 1152–3.

[8] Baillou A, Barin F, Allain JP, Pett E, Kocheleff P, Kadende P, Goudeau A. Human immunodeficiency virus antigenemia in patients with AIDS and AIDS-related disorders: a comparison between European and Central African populations. *J Infect Dis* 1987;**156**:830–3.

[9] Thiry L, Sprecher-Goldberger S, Jonckheer T, *et al.* Isolation of AIDS virus from cell-free breast milk of three healthy virus carriers. *Lancet* 1985;**i**:891–2.

[10] Ziegler JB, Cooper DA, Johnson RO, Gold J. Postnatal transmission of AIDS-associated virus from mother to infant. *Lancet* 1985;**i**:896–8.

[11] Lepage P, Van de Perre P, Caraël M, Nsengumuremyi F, Nkurunziza J, Butzler JP, Sprecher S. Postnatal transmission of HIV from mother to child. *Lancet* 1987;**ii**:400.

[12] Weinbreck P, Loustaud V, Denis F, Vidal B, Mounier M, de Lumey L. Postnatal transmission of HIV infection. *Lancet* 1988;**i**:482.

Correspondence to Dr P Lepage, Centre Hospitalier de Kigali, BP 879, Kigali, Rwanda.

Accepted 8 August 1988

Archives of Disease in Childhood, 1989, **64** 138–147

Short reports

Pyloric stenosis: congenital or acquired?

M D ROLLINS, M D SHIELDS, R J M QUINN, AND M A W WOOLDRIDGE

Department of Paediatrics, Altnagelvin Area Hospital, Londonderry, Northern Ireland

SUMMARY Pyloric muscle dimensions were measured in 1400 consecutive newborn infants. Nine of these subsequently developed pyloric stenosis. Their pyloric measurements at birth were all within the normal range. Congenital preformed muscular hypertrophy does not appear to be present in babies who later develop pyloric stenosis.

Infantile hypertrophic pyloric stenosis is usually classified as a congenital disorder. The condition is almost unknown in stillbirths, however, and usually presents with vomiting starting after the second week of life; this suggests that it may be acquired. Wallgren performed radiological examinations of the upper gastrointestinal tract of 1000 asymptomatic newborn infants and found that pyloric stenosis subsequently developed in five of them.[1] Barium studies performed in the newborn period showed no difference between the five who developed infantile hypertrophic pyloric stenosis and the others. The radiological studies, however, could not exclude a congenital preformed 'soft' hypertrophy of the pyloric muscle causing no constriction. Recently, two dimensional ultrasonography has proved reliable for confirming the diagnosis of infantile hypertrophic pyloric stenosis.[2] The purpose of this prospective study was to establish whether pyloric hypertrophy detected by ultrasonography is present at birth in infants who subsequently develop this condition.

Subjects and methods

Altnagelvin Hospital serves the population of Londonderry and adjacent areas of Northern Ireland. The study was carried out in the maternity and paediatric units of the hospital during the five month period from 1 January 1987 to 31 May 1987. The pyloric dimensions of 1400 consecutive newborn babies were measured at the time of their routine postnatal examination using an ADR 4000 scanner with 5·5 MHz transducer. This provided the normal range of newborn pyloric dimensions and a baseline from which to assess those who would later develop pyloric stenosis and present to this hospital. The ultrasound criteria for infantile hypertrophic pyloric stenosis used was of a pyloric anterior to posterior diameter ≥15 mm or muscle thickness ≥4 mm (figure).[3 4] Student's paired *t* test was used to

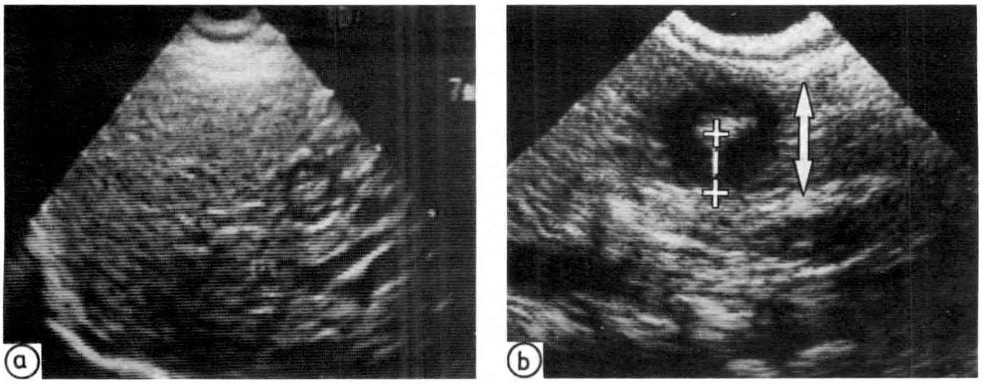


Figure *(a) Transverse sonogram. Normal pylorus of newborn. (b) Transverse sonogram. Characteristic 'target sign' of infantile hypertrophic pyloric stenosis. The distance between the crosses shows the thickness of the hypoechoic muscle mass. The cross section of the pylorus was also measured (anterior-posterior diameter).*

Table *Pyloric dimensions in infants studied. Results are mean (±2 SD)*

	Anterior-posterior diameter (mm)	*Muscle thickness (mm)*
Newborn infants (n=1391)*	8·8 (±2·2)	2·1 (±0·6)
Range	7·0–11·0	1·0–3·0
Infantile hypertrophic pyloric stenosis (n=9)	15·7 (±0·6)	4·9 (±0·14)
Range	13·0–23·0	4·0–6·0
Infantile hypertrophic pyloric stenosis (values on day 3) (n=9)	8·3 (±0·17)	1·8 (±0·09)
Range	7·0–10·0	1·0–2·0

*The nine infants later developing infantile hypertrophic pyloric stenosis were excluded from the normal range.

determine the significance of the change in pyloric dimensions from birth to presentation with infantile hypertrophic pyloric stenosis.

Results

A total of 1400 consecutive newborn infants had pyloric dimensions measured at routine postnatal examination. Nine of these infants subsequently presented to this hospital with infantile hypertrophic pyloric stenosis, which in all cases was confirmed by surgery. The pyloric dimensions recorded are summarised in the table.

The initial pyloric dimensions of the nine infants who presented with infantile hypertrophic pyloric stenosis were no different from the other 1391 healthy newborns. However, there was a highly significant increase ($p<0{\cdot}001$) in the size of the pylorus by the time infantile hypertrophic pyloric stenosis was diagnosed.

Discussion

This study shows that pyloric muscle hypertrophy is not present in the early newborn period of infants who later develop infantile hypertrophic pyloric stenosis. It excludes the possibility of a congenital preformed 'soft' hypertrophy of pyloric muscle without constricting effects suggested by Wallgren. The incidence of infantile hypertrophic pyloric stenosis in this study group was 6·4/1000 live births and is in keeping with the previously reported high rising incidence in this area.[5] We conclude that infantile hypertrophic pyloric stenosis should no longer be referred to as 'congenital' pyloric stenosis, although the true aetiology of this acquired condition remains to be elucidated.

References

1. Wallgren A. Preclinical stage of infantile hypertrophic pyloric stenosis. *Am J Dis Child* 1946;**72**:371–6.
2. Yip WCL, Tay SH, Wong HB. Sonographic diagnosis of infantile hypertrophic pyloric stenosis: critical appraisal of reliability and diagnostic criteria. *JCU* 1985;**13**:329–32.
3. Strauss S, Itzchak Y, Manor A, *et al*. Sonography of hypertrophic pyloric stenosis. *American Journal of Radiology* 1981;**136**:1957–8.
4. Blumhagen JD, Coombs JB. Ultrasound in the diagnosis of hypertrophic pyloric stenosis. *JCU* 1981;**9**:289–92.
5. Grant GA, McAleer JJA. Increasing incidence of infantile hypertrophic pyloric stenosis, 1971–1983. *Ir Med J* 1986;**79**: 118–9.

Correspondence to Dr MD Rollins, Department of Paediatrics, Altnagelvin Area Hospital, Londonderry, Northern Ireland.

Accepted 5 August 1988

Plasma aldosterone and renin activity

A M SCAMMELL AND M J DIVER*

*Institute of Child Health and *Subdepartment of Endocrine Pathology, University of Liverpool*

SUMMARY Eight infants had paired measurements of plasma aldosterone and plasma renin activity while being treated for congestive heart failure. There is parallelism with aldosterone and renin activity in the presence of a hyperactive renin-angiotensin-aldosterone system. Six patients had plasma renin activity and plasma aldosterone measured after commencing captopril and we have shown biochemical blockade of the renin-angiotensin-aldosterone system.

We have recently reported raised plasma renin activity in infants being treated for congestive heart failure due to congenital heart disease.[1] In that study we were unable to report the results of plasma aldosterone because concentrations fell outside the range of the assay in most instances. We have performed an additional study to determine whether parallelism between plasma renin activity and plasma aldosterone, which has been described in normal infants,[2] continues when the renin-angiotensin-aldosterone system is hyperactive, and whether this system can be blocked by using an angiotensin converting enzyme inhibitor.

Patients and methods

Eight patients had coincidental measurement of plasma renin activity and plasma aldosterone. Five of these patients had sampling on three separate occasions over a period of four weeks, one patient on two occasions, and two patients on a single occasion. The eight infants, at the time of the first sampling, had an age range of 19 to 111 days and their mean (SD) weight was 3330 (400) g. All the patients had congestive heart failure due to congenital heart disease with left to right shunts and were receiving diuretics.

Other criteria for inclusion in the study, the sampling conditions, and the method of estimation of plasma renin activity were as previously reported.[1]

Plasma aldosterone was measured by direct radioimmunoassay using a 'Coat-a-Count' kit with ^{125}I aldosterone label (Diagnostic Products Ltd). The antialdosterone antibody is coated on the walls of the assay tubes thus achieving solid phase separation of the bound and unbound fractions. Both intra-assay and interassay precision is less than 10% throughout the range of the assay. Samples with expected aldosterone concentrations greater than the working range of the assay were diluted in zero calibrator. This procedure had previously been validated by serial dilution of a high level sample that displayed parallelism with the dose response curve. One ml of whole blood was required for each of the assays.

Six patients, including two patients in the first study, were given captopril for treatment of their heart failure. The standard regimen in use at the Royal Liverpool Children's Hospital for initiating treatment was followed. Oral captopril was introduced at 0·25 mg/kg/dose three times daily. Increments of 0·25 mg/kg were made each day up to a maximum of 1 mg/kg/dose. Plasma renin activity and plasma aldosterone were measured after at least four days on the maximum dose. The same conditions were employed for blood sampling but in addition the sample was timed at two hours after the dose of captopril.

Results

A total of 14 paired plasma renin activity and plasma aldosterone values were obtained in the first part of the study. Three patients from the first batch of assays (6, 7, and 8) had only one set of paired values within the standards range (table). The results are plotted on the figure (triangles). The correlation coefficient by Spearman's rank test was 0·78 ($p<0·005$).

The patients in whom captopril had been administered showed an abolition of the relationship be-

Table *Sample times, plasma renin activity, and plasma aldosterone concentration, in eight patients*

Patient No	*Sample time (days)*	*Plasma renin activity (ng angiotensin I/ml/hour)*	*Plasma aldosterone (pmol/l)*
1	Zero	183	27 920
	6	81	21 070
	28	9	3630
2	Zero	88	29 910
	7	20	1690
	28	19	3010
3	Zero	69	12 810
	7	49	10 160
	28	25	2310
4	Zero	95	23 360
5	Zero	22	7770
6*	Zero	71	Outside standards range
	8	69	Outside standards range
	28	25	3026
7*	Zero	80	Outside standards range
	7	38	Outside standards range
	28	12	2359
8*	Zero	89	Outside standards range
	4	34	2388

Outside standards range: >3300 pmol/l; *=patients whose plasma aldosterone assays were performed without dilution.

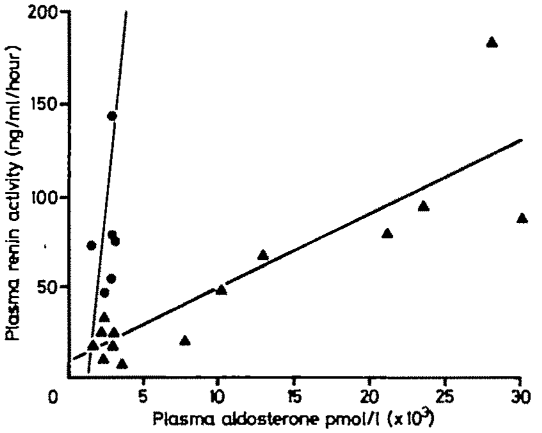


Figure *Plasma renin activity and plasma aldosterone in infants with congestive heart disease. Diuretic treatment without captopril (▲) and diuretic treatment with captopril (●).*

tween plasma renin activity and plasma aldosterone (figure, circles). There was no significant difference between mean (SD) plasma potassium concentrations before and after instituting captopril treatment (4·27(0·39) mmol/l and 4·33(0·51) mmol/l, respectively).

Discussion

This study has shown that there is parallelism with plasma renin activity and plasma aldosterone when there is hyperactivity of the renin-angiotensin-aldosterone system in infants in heart failure. Although five plasma aldosterone samples were above the range of the assay, these corresponded with high plasma renin activity values and tend to support our conclusion.

Previous studies of normal infants have shown good correlation with plasma renin activity and plasma aldosterone in the normal range.[2] In older children of widely varying ages with salt depleting conditions there is a rise of both plasma renin activity and plasma aldosterone.[3] By contrast exchange transfusion with acute blood volume loss results in increased plasma renin activity but no parallel rise in plasma aldosterone.[4] In our study the patients were in a stable state compared with those undergoing exchange transfusion.

The effect of captopril is to block the conversion of angiotensin I to angiotensin II. The latter is one stimulus to the production of aldosterone and our study would suggest it is the major stimulus in infants in heart failure. We have shown that captopril at a dose of 1 mg/kg can effectively block this hormone system. Further studies of infants being treated for heart failure are required to determine the minimum dose required for effective blockade.

We thank Mrs J Start and Mrs J Radcliffe for technical help with the assay procedures and the cardiology department at Royal Liverpool Children's Hospital, Myrtle Street for providing the patients for study.

References

[1] Scammell AM, Diver MJ. Plasma renin activity in infants with congenital heart disease. *Arch Dis Child* 1987;**62**:1136–8.

[2] Dillon MJ, Gillin MEA, Ryness JM, de Swiet M. Plasma renin activity and aldosterone concentration in the human newborn. *Arch Dis Child* 1976;**51**:537–40.

[3] Dillon MJ, Ryness JM. Plasma renin activity and aldosterone concentration in children. *Br Med J* 1975;**iv**:316–9.

[4] Dillon MJ, Rajani KB, Shah V, Ryness JM, Milner RDG. Renin and aldosterone response in human newborns to acute change in blood volume. *Arch Dis Child* 1978;**53**:461–7.

Correspondence to Dr AM Scammell, All Saints Hospital, Chatham, Kent.

Accepted 1 September 1988

Dysphagia due to oesophageal web

J W L PUNTIS,* S CHAPMAN,† D W PROOPS,† AND P SARTORI†

**Institute of Child Health, University of Birmingham and †The Children's Hospital, Birmingham*

SUMMARY An 8 year old boy developed a recurrent sensation of food sticking in his throat during meal times. Barium swallow examination showed an anterior oesophageal web at the level of C5. Symptoms disappeared after pharyngoscopy and dilatation of the web.

Case report

An 8 year old boy of mixed Asian and white parentage attended a school medical examination with a six month history of food sticking in his throat. He avoided eating meat, fish, eggs, and green vegetables, preferring soft foods that could be chewed easily. Frequent choking at mealtimes had lead to a decrease in appetite; liquids were tolerated without difficulty. Systematic enquiry showed no additional symptoms and the medical history was unremarkable. His parents and siblings were well and there was no family history of illness of any sort. Physical examination was entirely normal.

INVESTIGATIONS

Haematological investigation showed a normal haemoglobin (128 g/l), but a moderately reduced mean corpuscular volume (75·4 fl, reference range 80–96 fl) indicated probable mild iron deficiency. More detailed investigations were not undertaken at this time. A one month course of ferrous sulphate (120 mg three times daily) was given, and as dysphagia persisted, he was referred to hospital for further assessment.

Dysphagia had been present for 12 months at the time of hospital review. Clinical examination showed a thin looking boy with both height and weight on the third centile for age. There were no abnormal clinical findings. Haemoglobin was now 132 g/l and improvement in iron status was suggested by an increase in mean corpuscular volume to 83 fl. Measurements of serum iron, transferrin, and ferritin, together with platelet and reticulocyte counts were within the normal range. Repeated examination of stool specimens for occult blood was negative. Autoantibodies including antithyroid and parietal cell antibodies were not detected in the serum. A three day prospective record of food intake suggested a diet adequate in energy and protein but probably deficient in iron. Barium swallow examination clearly showed an anterior oesophageal web at the level of C5 (figure).

PROGRESS

On pharyngoscopy, appreciable pharyngeal narrowing due to an anteriorly situated web was confirmed. There was no evidence of malignant change. A biopsy specimen was taken from the web before successful dilatation. Histological examination showed acanthotic squamous epithelium with focal keratohyalin granule formation in the upper layers consistent with repeated mucosal trauma. No inflammatory changes were seen. At subsequent follow up the patient reported that his dysphagia had resolved.

Discussion

Postcricoid dysphagia is variously known as Paterson-Kelly syndrome, Plummer-Vinson syndrome, or sideropenic dysphagia. Paterson reported the association, usually in women, of dysphagia and glossitis and remarked upon an increased risk of malignancy occurring in the upper oesophagus, while Brown-Kelly found that some patients had a web in the cervical oesophagus and noted an association with anaemia.[1] The web generally consists of a thin fold of mucous membrane, as in our patient. A review of the literature suggests that the syndrome has only once previously been reported in a child.[2] This was in an anaemic 15 year old girl in whom the diagnosis of oesophageal web was made only on the occasion of her third admission to hospital for investigation of dysphagia. Knowledge of Paterson-Kelly syndrome therefore is almost exclusively derived from studies of adults. Our case is of particular interest both because the child is male and of very young age.

Although it is not essential to find evidence of iron deficiency before making a diagnosis of Paterson-Kelly syndrome,[3] some studies have shown it to be strongly associated with postcricoid web, and have lead to the conclusion that iron deficiency, commonly due to blood loss, plays some part in the pathogenesis of the web.[4] Clearly, evidence for iron deficiency was slight in our patient and gastrointestinal blood loss excluded. We therefore suspect that the mild iron deficiency was not implicated in the web formation and may have been a consequence of poor dietary intake resulting from dysphagia. As webs are so infrequent during childhood, a period in which iron deficiency is commonly described, it may be that duration of anaemia is more significant than anaemia itself.

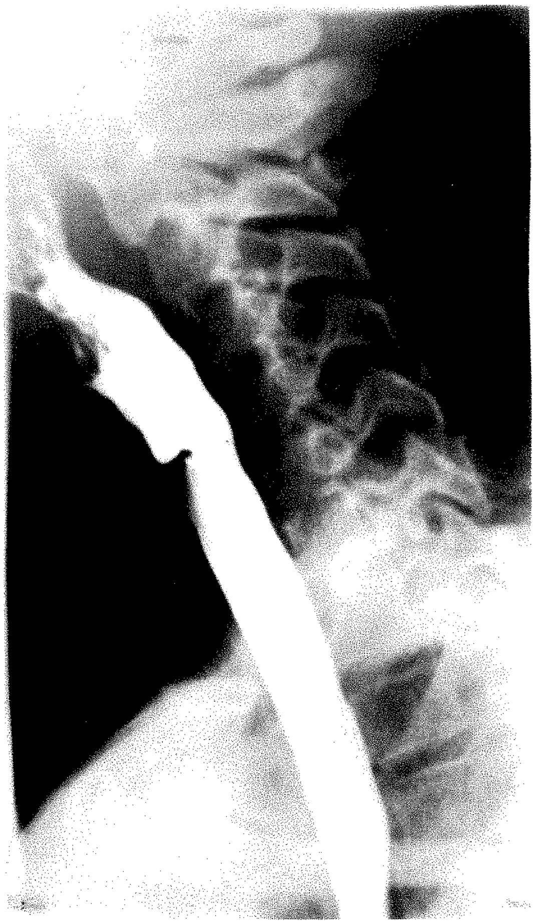


Figure *Barium swallow showing anterior oesophageal web at the level of C5.*

Webs can exist without giving rise to symptoms and as many as 10% of adults with iron deficiency but without dysphagia may be shown to have postcricoid webs on barium swallow.[5] Thyroid disease, thyroid antibodies, and malignant disease of the upper gastrointestinal tract are more common in iron deficient patients with webs than those without, suggesting that autoimmunity is a factor in Paterson-Kelly syndrome. It is reported that treatment with iron and correction of anaemia may sometimes relieve dysphagia but without necessarily altering the radiological appearance of the web itself. Whether such treatment has any effect on the estimated 5% risk of malignant change in the pharyngo-oesophageal region is uncertain.[4]

Oesophageal web remains an uncommon cause of dysphagia in childhood but one which may be suggested by careful history taking and clinical examination. Barium swallow can be diagnostic but false negative or misleading results sometimes occur particularly if reluctance to drink the barium results in poor dilatation of the pharynx insufficient for the web to be visualised.[2] The lack of information regarding postcricoid dysphagia in childhood makes the prognosis for our patient impossible to define. When the diagnosis is not made until adult life there may be a history of dysphagia going back to childhood. One such case, a male diagnosed at the age of 38, developed squamous cell carcinoma of the pharynx 10 years later.[6] Our patient has so far only been followed up for a few months but as the risk of malignancy is particularly worrying in a young child we plan to keep him under regular review with repeat pharyngoscopy at six monthly intervals, whether symptomatic or not.

References

[1] Brown-Kelly A. Spasm at the entrance to the oesophagus. *J Laryngol Otol* 1919;**34:**285–9.

[2] Klifto EJ, Allen SK, Metzman M, Chase PJ, Kupersmit M. Plummer-Vinson syndrome: report of a case and review of the literature. *Journal of the American Osteopathic Association* 1983;**83:**56–9.

[3] Wynder EL, Fryer JH. Etiologic considerations of Plummer-Vinson (Paterson-Kelly) syndrome. *Ann Intern Med* 1958;**49:**1106–28.

[4] Chisholm M, Ardran GM, Callender ST, Wright R. A follow-up study of patients with post-cricoid webs. *Q J Med* 1971;**40:**409–20.

[5] Chisholm M, Ardran GM, Callender ST, Wright R. Iron deficiency and autommunity in post-cricoid webs. *Q J Med* 1971;**40:**421–33.

[6] Logan J S. A review of the Plummer-Vinson stricture of the cervical oesophagus. *Ulster Med J* 1978;**47**(suppl 2):1–14.

Correspondence to Dr J W L Puntis, Institute of Child Health, Francis Road, Edgbaston, Birmingham B16 8ET.

Accepted 26 August 1988

High compared with standard dose lipase pancreatic supplement

P J ROBINSON,* A OLINSKY,* A L SMITH,† AND S B CHITRAVANSHI‡

**Professorial Department of Thoracic Medicine and †Department of Gastroenterology, Royal Children's Hospital, Melbourne, Australia, and ‡Medical Services, Organon International, The Netherlands*

SUMMARY Cotazym-S-Forte, a new pancreatic supplement containing 10 000 BP units of lipase activity per capsule, was compared with a standard dose pancreatin supplement (Pancrease) with 5000 BP units lipase activity in a randomised crossover trial. The number of capsules of Cotazym-S-Forte administered was half the usual number of Pancrease capsules and was associated with the same degree of fat absorption as Pancrease.

Relative deficiency of exocrine pancreatic enzymes occurs in about 85% of patients with cystic fibrosis.[1] Within any group of patients with cystic fibrosis there is a wide range of requirements for pancreatic enzyme supplements.[2] The large number of capsules required by some patients may contribute to poor compliance. If the number of capsules could be reduced while maintaining adequate fat absorption this would be of benefit to the patients.

The aim of this present study was to compare a high lipase dose, enteric coated, enzyme supplement (Cotazym-S-Forte (Organon), 10 000 BP units lipase activity per capsule) with a standard lipase dose enteric coated, enzyme supplement (Pancrease (Cilag), 5000 BP units lipase activity per capsule). It was reasoned that the same degree of fat absorption could be achieved with half the number of capsules. This study was performed to test this hypothesis.

Patients and methods

Thirty patients with cystic fibrosis (20 boys, 10 girls) ranging in age from 1·3 years to 13·8 years (mean 4·7 years) participated in the study. Each patient had classic features of cystic fibrosis and a sweat chloride concentration >60 mmol/l on pilocarpine iontophoresis. At entry into the study all patients were taking Pancrease.

The study consisted of two 14 day periods, one while taking the usual dose of Pancrease and the other while taking Cotazym-S-Forte. The number of Cotazym-S-Forte capsules was calculated to be half the usual number of Pancrease capsules. When the number of Pancrease capsules was an odd number the lower half was taken. Patients were randomly allocated to commence with either Pancrease or Cotazym-S-Forte. Sixteen patients took Pancrease in the first 14 day period of the study and 14 Cotazym-S-Forte. Each 14 day period terminated with a three day fat balance study performed at home. This consisted of a full dietary recording for four days with a faecal collection during the last three days of this period. No restriction was placed on fat intake during the study period. As a further check that the fat intake was similar in both periods and represented by the dietary record at the end of the period, however, a further two days of dietary recording was performed mid way through each 14 day period separate from the recording period for the fat balance study.

Faecal fat estimation was calculated using the acid titration method of van de Kramer *et al.*[3] Fat content of ingested foods was calculated from the dietary records using the Microdiet software package (Department of Mathematics and Statistics, University of Salford, United Kingdom). Where necessary, additional foodstuffs were added to the programme using values from Australian dietary references.[4 5] The percentage of fat malabsorbed was calculated by the equation:

$$\%\ \text{Fat malabsorbed} = \frac{\text{Three day fat output (g)}}{3\times\text{Mean daily fat intake (g)}}$$

Fat malabsorption values on each supplement, average number of capsules taken for the 14 day period, and fat intake during periods when faecal collection was, and was not performed, were compared using the paired *t* test. The study was approved by the hospital ethics committee and written parental consent was obtained.

Results

Twenty five patients successfully completed the 28 day study period. One patient taking Cotazym-S-Forte withdrew from the study after developing diarrhoea. Three patients were excluded because of incomplete and inaccurate dietary recording and a further patient was withdrawn due to incomplete faecal collection. There was no significant difference between the fat input during periods of faecal collection and periods during the two week study period where dietary recording was performed without faecal collection. The degree of fat malabsorption while taking Pancrease and Cotazym-S-Forte was not significantly different (figure). The mean degree of malabsorption while on Pancrease was 12% and on Cotazym-S-Forte 13%. The group mean intake for Pancrease was 31 capsules a day (range 10–56), while for Cotazym-S-Forte the figure was 14 capsules a day (range 6–25). This represents an average daily lipase input of 15 500 units (range 5000 to 28 000 units) while on Pancrease, and 14 000 units (range 6000 to 25 000 units) while on Cotazym-S-Forte.

Discussion

The results of the present study have shown that Cotazym-S-Forte is as effective as Pancrease in reducing the fat malabsorption in patients with cystic fibrosis. Cotazym-S-Forte has the added advantage that the number of capsules needed are half that of Pancrease. It would therefore be of benefit to those patients who require large amounts of pancreatic enzyme supplements to correct their fat malabsorption. Reducing the number of capsules would probably also lead to greater compliance with

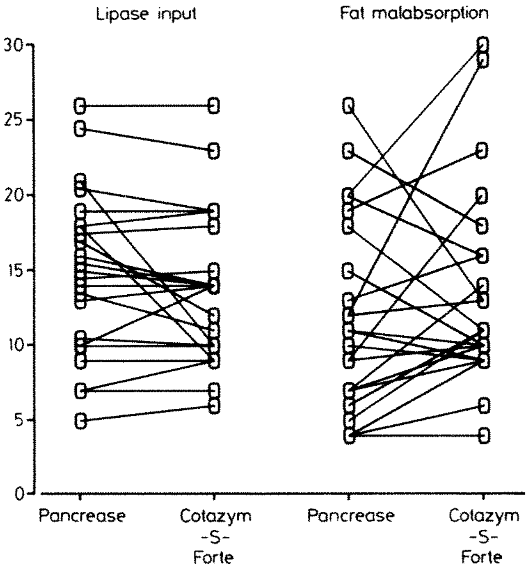


Figure *Left: average daily lipase input (1000s of international units) during the two periods of faecal collection. Right: fat malabsorption, as a percentage of ingested fat, while taking Pancrease and while taking Cotazym-S-Forte.*

the medication. Despite instructions to reduce the number of capsules by only half when taking Cotazym-S-Forte, some patients reduced it by more than half without any significant alteration in fat malabsorption. This does not negate the results of this study as the aim of this study was to determine if Cotazym-S-Forte was as effective as Pancrease, not that it necessarily had better activity.

Individual microspheres of Cotazym-S-Forte have a mean (SD) diameter of 1·2 mm (0·4 mm), (personal communication, Organon) a size smaller than the average quoted size for Pancrease microspheres, <3 mm (product information, Cilag). Meyer *et al* have shown that while sphere size in the 1–3 mm range determines the rate of emptying from the stomach (independent of meal composition), microspheres should be in the range of 1·4 (0·3) mm to empty at the same rate as emulsified food. (Meyer J, Elashoff J, Porter-Fink V, Dressman J, Amidon G. What should be the size of pancreatin microspheres? Abstract presented at the American Gastroenterological Association Meeting, Chicago, May 1987.) Thus the microsphere size may be the reason why some patients were able to reduce their capsule intake to less than half their usual Pancrease dose without an alteration in the degree of fat malabsorption. Another possible and more likely explanation for the reduction in enzyme intake by more than half is that these patients were taking an excessive number of Pancrease capsules initially.

All patients involved with the study expressed preference for the Cotazym-S-Forte preparation due to the reduced number of capsules required. No side effects were noted. The diarrhoea experienced by one patient while on Cotazym-S-Forte is unlikely to have been a side effect as several members of his family, who do not have cystic fibrosis, had similar symptoms at the same time. The preparation appears to be safe and acceptable.

With the advent of enteric coated pancreatic supplements our ability to provide adequate nutrition in cystic fibrosis has improved due to the greater utilisation of fat as an energy source. While it remains likely that in the foreseeable future enzymes will still be needed, a reduction in the number of capsules required would be of major benefit to these patients.

The results of this study have shown that Cotazym-S-Forte is as effective as Pancrease in correcting fat malabsorption in cystic fibrosis and has the added advantage of needing only about half the number of capsules.

The authors wish to thank Organon for their help with the project. They also wish to thank Mrs B Crawford who performed the faecal fat assays.

References

[1] Wong LT, Turtle S, Davidson AG. Secretin pancreozymin stimultation test and confirmation of the diagnosis of cystic fibrosis. *Gut* 1982;**23**:744–55.

[2] Graham D. Ins and outs of pancreatic enzymes and adjuvant therapies. *J Pediatr Gastroenterol Nutr* 1984;**3**(suppl 1):S120–6.

[3] Van de Kramer JH, ten Bokkel Huiniak H, Weyers HA. Rapid method for determination of fat in feces. *J Biol Chem* 1949;**177**:347–55.

[4] Greenfield H, ed. The nutrient composition of Australian meats and poultry. *Food technology in Australia*. 1987;**39**: 181–240.

[5] Thomas S, Corden M. *Metric tables of composition of Australian foods*. Canberra: Commonwealth Department of Health Food and Nutrition Section, 1977.

Correspondence to Dr PJ Robinson, Professorial Department of Thoracic Medicine, Royal Children's Hospital, Flemington Road, Parkville, Victoria 3052, Australia.

Accepted 11 August 1988

Spontaneous regression of congenital epulis of the newborn

H R JENKINS AND C M HILL*

*Departments of Child Health and *Oral Surgery, University Hospital of Wales*

SUMMARY An infant with congenital gingival epulis which spontaneously regressed over the first year of life is reported. A policy of conservative management should be adopted in this condition unless there are feeding problems in the newborn period or reasons to doubt the diagnosis.

Congenital epulis of the newborn is a rare, benign tumour of the gingiva first described in 1871.[1] The aetiology and histological origin of the tumour are unknown and there are still doubts as to the natural history of the condition. The optimal management of congenital epulis is unclear and some authors have recommended simple excision in the neonatal period.[2] This report concerns an infant who presented with a congenital epulis arising from the anterior maxillary region that was managed conservatively. Subsequently there was spontaneous regression of the lesion during the first year of life.

Case report

A girl, weighing 3900 g, born at term by spontaneous vertex delivery after an uneventful pregnancy was noted to have a pedunculated, fleshy mass measuring some 1·5 cm in diameter arising from the right anterior alveolar margin (fig 1). There was no family history of congenital abnormality and the child was otherwise normal. Despite the size and prominence of the mass the infant fed satisfactorily from the breast and subsequently thrived.

Surgical excision was deferred and the child was reviewed regularly on an outpatient basis. There was spontaneous regression of the epulis to a size of 3–4 mm by 12 months of age (fig 2). The primary dentition erupted uneventfully.

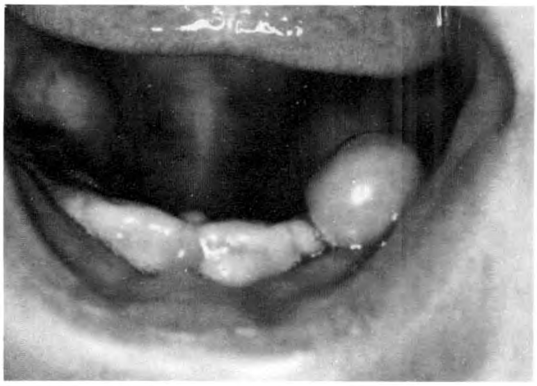


Fig 1 *Congenital epulis of the newborn photographed five days postpartum.*

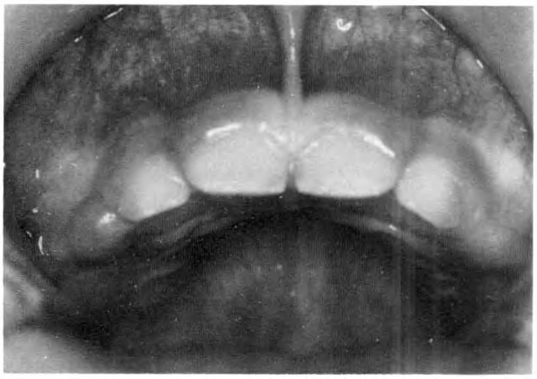


Fig 2 *The same lesion 12 months later adjacent to the upper right deciduous lateral incisor ($\underline{B|}$), virtually indistinguishable to the untrained eye.*

Discussion

Approximately 120 cases of congenital epulis of the newborn infant have been described in the literature since the first report in the 19th century,[1] and several important features have emerged. In a review of the 113 cases described between 1871 and 1971 Fuhr and Krogh noted a striking and unexplained preponderance of females, with the maxilla affected two to three times as often as the mandible.[3] Rarely multiple lesions have been decribed with associated abnormalities of the nasal bridge and septum.[4]

The clinical diagnosis of congenital epulis is almost obligatory when a solitary tumour of the gingiva is present at birth. The diagnosis can only be confirmed by histological examination but this would involve surgical intervention, with the attendant risks of haemorrhage in a small neonate, and negate the conservative approach that some authors have advocated. The remote possibility of Epstein's pearls (gingival cysts) or of an eruption cyst arising prematurely would not be consistent with the clinical characteristics of the lesion which is pink, rubbery firm, and present at birth. The other possible diagnosis is that of an isolated premature nodule of fibromatosis gingivae but the subsequent clinical history in our case was not consistent with this.

There are no reports of recurrence of congenital epulis after excision, or of metastasis, and the histological appearance of the lesion is usually that of a granular cell myoblastoma without pseudoepitheliomatous hyperplasia.[5] The aetiology of the condition is unknown, and the natural history and optimal management of the lesion are not well defined. Most cases of congenital epulis are treated surgically and some texts recommend early excision of the lesions in the newborn period.[2]

Despite the fact that this lesion is probably hamartomatous and neither inflammatory nor neoplastic, excision of a sessile epulis may expose a wide base which can bleed persistently and in early infancy precautions must be taken to limit blood loss to an absolute minimum. Parenteral vitamin K, atraumatic intubation, the use of local anaesthetic with vasoconstrictor, excision without margins, and bipolar coagulation should all be employed if surgical excision is indicated. Welbury,[6] however, has advocated an expectant, non-operative approach as the management of choice and, having adopted this policy in our case, there was considerable spontaneous regression of the lesion by the age of one year. Alveolar development and the early dentition appear to have been unaffected.

It may well be that congenital epulis of the newborn is not as rare as has been previously believed and perhaps, with a greater awareness and reporting of the condition, its natural history will become more evident. In the meantime, contrary to the opinions of some authors, we would strongly advocate a conservative approach to the lesion unless there are feeding problems or diagnostic doubt that necessitate surgical intervention. If there are obvious and troublesome feeding difficulties in the newborn period simple excision with the precautions outlined above is the treatment of choice.

We wish to acknowledge the help of the department of medical photography at the University College of Wales Dental School for producing the illustrations and also Mrs Carole Demontoux for typing the manuscript.

References

[1] Neumann E. Ein fall von congenitaler epulis. *Arch Heilkunde* 1871;**12**:189.
[2] Dilley DH, Blozis GC. Oral lesions and oral manifestations of systemic illnesses. *Pediatr Clin North Am* 1982;**29**:587–9.
[3] Fuhr AH, Krogh PHJ. Congenital epulis of the newborn: centennial review of the literature and a report of case. *Journal of Oral Surgery* 1972;**30**:30–5.
[4] Rainey JB, Smith IJ. Congenital epulis of the newborn. *J Pediatr Surg* 1972;**19**:305–6.
[5] Cussen LJ, McMahon RA. Congenital granular-cell myoblastoma. *J Pediatr Surg* 1975;**10**:249–53.
[6] Welbury RR. Congenital epulis of the newborn. *British Journal of Oral Surgery* 1980;**18**:238–43.

Correspondence to Mr CM Hill, Department of Oral Surgery, Cardiff Dental Hospital, Heath Park, Cardiff CF4 4XY.

Accepted 11 August 1988

Archives of Disease in Childhood, 1989, **64,** 148–149

Controversy

Shared care in paediatrics

C J BACON

Department of Paediatrics, Friarage Hospital, Northallerton

I work with one consultant colleague in a district general hospital about 50 miles from the nearest regional centre, which is Leeds. All children in the district with a serious illness initially come to us and an important principle in our work is the need to be aware of our limitations and when to ask for help. A good working relationship with regional colleagues is vital.

The life blood of this relationship is the telephone. When you are worried about a child with an unfamiliar or deteriorating illness it makes all the difference if you discuss things over the phone with a specialist colleague, preferably someone you already know well so that you are at once on the same wavelength. For example if you are watching a child with acute renal failure an early call to the nephrologist will enable you to make calmer decisions about dialysis and less rushed arrangements for transfer; parents too will be reassured to know that you are in touch with a specialist from the outset. For the relationship to thrive the regional specialist must make himself accessible to phone calls; if he dislikes carrying a bleep he must have a sweet voiced secretary who can track him down and persuade him to phone back without delay.

In chronic conditions the sharing of care between a peripheral and a regional paediatrician involves the same principles as it does between a general practitioner and a consultant. At an early stage it is helpful for the specialist to carry out a comprehensive assessment; thereafter there may be routine periodic reassessments and help during crises. The local man, however, should remain responsible for overall management and day to day care. He is in a far better position to assess the family and social background, to organise various support services, and to cope with any coincidental problems.

With these principles in mind we have developed arrangements with regional specialists in cardiology, endocrinology, respiratory disease (especially cystic fibrosis), nephrology, and paediatric surgery. We usually refer the children to Leeds for initial assessment and sometimes institution of treatment. They then come back to our care, but have specialist reassessment at intervals varying from three months to two years, according to the type and severity of their problems. Whenever possible these reassessments are done at a combined clinic at our own hospital. These combined clinics are a vital ingredient of shared care, and have advantages for all concerned: the families do not have to travel so far and perceive that their local paediatrician and the regional specialist are truly in concert; the local paediatrician learns a lot and feels more involved in major decisions; and the regional specialist has a pleasant outing in the country—and ensures himself a steady flow of referrals and research material.

Shared care of neonates calls for particularly close understanding. As a matter of policy our unit maintains a capability for only short term ventilation, and babies likely to need intensive care for more than a few hours are transferred to one of the two regional units. An ability and a willingness always to accept such transfer is an essential basis to the relationship. The regional units send out highly efficient teams to collect very preterm babies who have evaded transfer in utero. The team takes about 90 minutes to arrive, during which time we do our best to get the baby in good condition for travel and to support the parents. The handover, usually from peripheral consultant to regional registrar, calls for tact on both sides, the former bowing to the other's sharper skills, the latter not flaunting them too aggressively. If the units know and respect each other's capabilities, babies can be transferred back as soon as intensive care is no longer needed, freeing the regional unit cot and making life easier for the family. After discharge routine follow up can be at the district general hospital, with an occasional visit to the regional unit if it wishes to monitor outcome.

Some specialties, for example oncology and renal transplantation, call for continuing close supervision by the regional unit, though here too there is a place for a local contribution. It is thoughtless to get a child to make a 100 mile round trip for a routine blood test when there is a district general hospital just down the road. Regional units sometimes justify this behaviour by saying 'The family prefers to come to us'. In fact this denotes a failure on the part of the regional unit to encourage trust in the district general hospital; it is only too easy, and extremely damaging, for the regional unit to give the impression that the district general hospital cannot give the required standard of care. When tempted to make such an aspersion the clever regional registrar should remember that the consultant at the district general hospital was once in the same position.

What peripheral paediatricians dislike most is having their patients taken over by a regional specialist who cuts them out of management. Such a specialist must not be surprised if he gets only one referral from each colleague.

I once phoned a supraregional unit over 200 miles away for advice on a rare illness and was instructed to send the child to them forthwith; another unit, soon contacted instead and always used since, helpfully guided me in managing the child on my own ward. It is also annoying for a paediatrician in a district general hospital to be bypassed, either by a general practitioner who refers direct to the regional unit, or by one regional unit referring on to another when the family moves house; the remedies here are in the first case a quiet chat in the bar, and in the second acknowledgment by the regional unit that the local man should also be involved. I am always happy for a colleague with a special interest to see my unusual cases—so long as he does not poach them—and to write them up if he wishes; it is gratifying to be asked first, and even more gratifying to be given the opportunity to decline joint authorship.

As a frequent recipient of helpful advice I have come to appreciate the art of imparting it tactfully. I want my knowledge extended and my errors put right for the future, but if my nose is rubbed too hard in my ignorance and mistakes I might take fright next time. I am irritated by the hypocritical 'as you knows' and 'of courses' with which medical letters are larded. I prefer my advice cold turkey, but for those who like some dressing, a useful ploy is to shift the imputation of ignorance and preface information with 'I told the parents that . . .'.

Taking politeness one stage further, one much respected regional colleague always starts his letters 'I quite agree that this is . . .' no matter how wildly different one's suggested diagnosis: he gets a lot of referrals.

A good relationship between peripheral and regional paediatricians has to be worked at. It requires mutual respect and courtesy, and a proper humility. The local man must acknowledge that it is his duty to obtain for his patients the best knowledge and skills available and that in this day and age these cannot all reside with him. The specialist must accept that his omniscience may not extend beyond his specialty and that many things may best be done locally. Once achieved a good relationship will be rewarding for both sides, and above all will bring the greatest benefit for the families they are trying to help.

Correspondence to Dr CJ Bacon, Department of Paediatrics, Friarage Hospital, Northallerton, North Yorkshire DL6 1JG.

Archives of Disease in Childhood, 1989, **64,** 150–154

Families with congenital heart disease

J L EMERY

Wolfson Unit, Department of Paediatrics, University of Sheffield

SUMMARY Families with congenital heart deformities appear to have more difficulties and stress than those with other deformities. Some problems are intrinsic to the deformity but others are largely related to communication difficulties between the groups doing home support and those in supraregional centres.

Any child born with a deformity or disorder that seems either life or career threatening produces anxieties and distress. Congenital deformity of the heart is now the largest single group of gross congenital deformities, and their families have special problems. Some of the problems that occur in their homes are discussed here; this paper is based on personal experience with bereaved parents over a 40 year period.

It was my practice as a children's pathologist to talk face to face with parents of children on whom I had carried out necropsies. During a total of about 7000 child necropsies, I probably saw the parents of nearly a half. Furthermore, in the hospital we developed a system whereby a specially trained mortuary attendant handled the child and talked with the parents in a humane way. Parents talked to this non-medical woman over a cup of tea in a way that they would never talk to me in my office.

During the past 15 years our interests have become increasingly focused on home deaths rather than hospital deaths and we have been carrying out confidential enquiries at increasing depth on all baby deaths from the age of 2 weeks to 5 years The home visits started with the cot deaths and when some others were visited as controls it became immediately obvious that people would say things at home that they would not mention in hospital. This particularly applied to personal relationships with their relatives and friends.

An enquiry technique has been developed with Dr Elizabeth Taylor, and the amount of information obtained at conferences in the general practitioner's surgery after these visits is of a completely different order to that obtained previously from interviewing the parents in hospital or by holding a hospital case conference.

Unexpected postneonatal deaths

Congenital heart disease presents to families in two forms; children who present symptoms and are diagnosed in the lying in hospital very soon after birth, and children who are apparently completely normal at birth but present three or four weeks later either as failure to thrive or as unexpected deaths. In any series of children presenting as unexpected deaths in the postneonatal period (cot deaths), there is always a group of children with congenital deformity of the heart and these constitute perhaps about one in 20 of children who so present. The death of these children is unexpected by the parents, although in most cases when one analyses the history from the point of view of gaining weight or symptomatology, some abnormalities in the child's development have been present but not recognised. Before the 'cot death syndrome' became popular, to diagnose an unexpected death as a congenital deformity of the heart was usually a relief to the parents as it constituted an adequate explanation for the death. Now the situation has altered. Parents of virtually every baby who is found unexpectedly dead are now presented with the literature on cot deaths in the hospital receiving rooms or by health visitors, usually before a necropsy has been carried out. When a diagnosis of a congenital deformity of the heart appears, it often disconcerts the parents. There is now a wide public awareness of dramatic surgery on babies' hearts but only successes gain publicity. Parents immediately question themselves as to whether they have missed something and whether, but for some action on their part, the child could have had a life saving operation. Once the diagnosis of congenital heart disease is made, the family is removed from the 'cot death' classification and the whole of the cot death bereavement and surveillance support network from these people is also removed. There is no other system to take its place. These children have not been under the care of any cardiology unit. As pathologists or paediatricians we can arrange for these parents to have genetic counselling regarding the possibility of further children with congenital heart disease, but this is only of marginal emotional assistance to them. These parents are just as anxious about another child death with their next pregnancy as are classic cot death families and need at least as much support.

Acceptance of a diagnosis

In most children congenital heart disease is suspected in them as newborns and then diagnosed. The situation is similar in general ways to the other major group of congenital deformities, namely children with hydrocephalus and spina bifida, but has differences. Both groups have the shock of loss of expectation and of accepting this—for example, 'Why me and my child?'—and the insecurity of the future. There is often delayed separation of the baby from the family and friends with a distorted growth pattern of 'love' between the family and the child. If the child is kept in hospital with one parent, there is again the distortion in the pattern of love. As the existence of the deformity becomes accepted, there follows the anxiety for the child in older age and financial implications. With the knowledge of increased dependency there is then a growth of emotional attachment to this child with essential compensation and possibly over compensation facets. All these aspects apply to all children with defects, but with the child with the heart deformity there is an added difficulty in acceptance. The child that has spina bifida or hydrocephalus usually has some degree of talipes or other physical deformity that the parent can recognise and so actually sees that the child is deformed, whereas the child with congenital deformity of the heart is often overtly completely normal. The child may be pale or cyanosed but parents are not as familiar with concepts of cyanosis and pallor as physicians and these, in my experience, have very little meaning to them, particularly if it is their first child. Thus the child is to them a normal child but the doctors have been able to recognise that the heart is abnormal.

Doctors often spend a lot of time with parents explaining the anatomy of the heart, they show them ultrasound studies, and *x* ray studies, and models of the heart. This is very difficult for all but the very rare parent. The parents are not basically interested in anatomy, although they appreciate that the doctors, and particularly the surgeons, are fascinated by it. Parents frequently tell the doctors that they understand exactly what they are describing when they do not. The only thing parents are interested in is whether the child will grow up as a normal child or not. On this point the physicians and cardiologists are always careful not to make a prognosis of complete normality. The parents are carried along on a wave of need to investigate, which they try to understand, but they are still in a sort of 'zombie' state of growing acceptance. During this time the babies are lifted from their home base to supraregional investigatory and treatment centres. In such places modern medical magic takes place and the oracles there come out with a verdict that goes down the familial line—treatment/non-treatment, immediate surgery or not.

Different children need different patterns of care. Some children are sent home to die, most go home under supervision to return for staged surgery, some go home directly, and others go to the units from which they were referred. There are problems regarding all these aspects and it is probably simplest to take them separately.

Special units

LEVELS OF CARE: UNIT, LOCAL HOSPITAL, AND HOME

Highly specialised supraregional units, whether for congenital deformities of the heart or other special disease, create as well as solve problems. They are usually staffed by brilliant people who are enthusiasts, some would call them 'fanatics', and gather round them a group of people who they are able to infect with their enthusiasm. This produces a level of concentration and interest in the patient that is not available elsewhere. Therein lies the very value of such units and why they can attain such high technical excellence. Parents recognise this enthusiasm, they see it as a special interest in their own child and the doctors and staff of such institutions become a sort of priesthood to them. It is part and parcel of all such units to know how good they are, to tell each other how good they are. This is all part of the psychology of running any good unit. When a child is returned from such a unit back to its base hospital it is impossible for the parents not to be aware that the child is going back to a lower level of care and attention. No matter how good the original referring unit was, it has not the egocentricity relating to that child's condition that is present in the special unit. This creates problems of confidence for the parents of the referred child. It is not easy for the nursing and medical staff of the base units to handle the situation, everything in a way mitigates against the parents. The child in the ward is not the consultant's whole responsibility and it is very difficult for a relative lack of interest not to become apparent. All know that the child had to go to another place for 'special tests' and that the major decisions relating to treatment have been determined from outside. Parents often express to us at home how frustrated they are at what appears to them to be defects in local care, which is in actuality not different from what took place in the specialist unit. They are afraid to say anything or make dissatisfaction known to the local staff because they feel they are completely in their hands.

If the child is sent home rather than to the hospital, the situation is often less difficult but there are frequently great problems in communication. There is a timing situation which is very difficult to overcome. If a child is being sent home a referral letter needs to be sent. This usually goes to the referring unit or referring doctor. Such a letter usually takes four or five days. This produces a delay of about 10 days in getting detailed information about a patient to the people who are looking after the child at home. Some units attempt to convey information to the local people by telephone, some have a special liaison health visitor or social worker staff to do this but this works only in a partial way. Telephone information about a child who is only slightly known to either person is difficult, and to catch and speak to the child's health visitor and family doctor entails a use of time that very few units can afford. If this type of information is relayed to the local hospital liasion staff this only creates another stage in which information is reduced in interest and urgency. The need for a formal letter remains. Currently children arrive home and the local health visitor and family doctor don't know that the baby is home until the parents come for help and information. Without a detailed letter of findings and instructions in hand, both the family doctor and the health visitor are at very great disadvantage. Some units send the parent home with duplicate letters giving information for the health visitor and family doctor. This is by far the best method of handling the situation but some units do not want parents to read what they feel are confidential letters and so will not do this. I am convinced that they are wrong in this. I know of one unit where the ward sister always sent a hand written note by the mother to the health visitor—which worked excellently. We have come across several instances where the child coming home produced quite dangerous levels of difficulty in home care, and some cases where we believe that children have died unnecessarily because of hospital staff not being aware of the precise home situation. There are often tensions and factors at home that parents hide from hospital staff and hospital social workers, particularly if parents want the child home.

ACCESSIBILITY AND COST OF VISITING

The special units have also another problem in that of ease of accessibility to the family. I well remember when visiting one unit and discussing the family situation with the paediatricians there who said how nice it was to work in a unit where both parents brought the child to the unit on every occasion. This was presented as a sign of excellent communications and care of the child. But seen from the other side the situation was quite different. This unit was so isolated and distant from the child's home that it was virtually impossible to reach it except by car. Special units are very rarely sited at city centres but more usually at some previous isolation unit. One parent cannot take a child in the car by themselves so both parents have to go, and in many instances the father has to take the day off work and lose salary in order to take his wife to a special care unit. Some families can ill afford this. In our community less than half of the parents have cars of their own and so visits necessitate either lengthy journeys involving taxis or persuading some friend or relative to drive the car for them. There are some voluntary organisations that do help in this way but these are not usually automatically laid on.

When the child is admitted to a special unit additional problems of time and expense occur. Overnight accommodation is sometimes provided by the unit but by no means always. It is difficult enough for grandparents and siblings to attend local hospitals when children are admitted but attending distant hospitals is very difficult indeed. We have known grandparents not go to see the children in hospital, but pay for the parents to go, thinking that it is better for the child to see the parents than themselves. We have seen parents go into considerable debt in relation to the cost of travelling to see their children in distant units. It is the middle class parent who is at greatest disadvantage as the extremely poor parent on public assistance usually is able to get assistance and asks for it, whereas the young professional has equal difficulties and often more responsibilities. When the NHS has 'rationalised' services, I have never known the additional cost to the families to be taken into account. We hear stories of families in the United States going into debt, selling their houses and cars because their children need special high cost care but the same does occasionally happen within our own NHS and, with current trends, this could well increase.

SURGERY THAT IS NOT SUCCESSFUL

Surgeons are at great pains always to point out that surgery is not always successful, and the patient may die if not during the operation, soon afterwards. The parents sign a certificate to permit the operation but while they hear the words that the surgeon says, they have accepted the situation usually in a different way. The surgeon to them is to some extent the hand of the Almighty, they know that he knows that he is not successful every time but they also know that, or at least they think they know, he firmly believes that on this occasion there will be success, and thus although there is a theoretical intellectual acceptance that the child may not survive, it is not an emotional acceptance. Optimism is the name of the game. If the child dies the world falls apart in a way that is greater than if a child dies from an operation related to cancer or something that is known to be lethal in the emotional sense. If the child dies, the surgeon is usually at pains to explain to the parents why the operation failed. It is very difficult for the surgeon not to justify things to himself in what he is saying to the parents, and it is commonplace for the parents to come away from their interview with the physicians and surgeons and make a remark to their friends as to 'how sorry they are for the surgeon' that he was not able to be successful in this instance. Deaths in baby heart surgery are more difficult than in other situations because quite frequently the child has been built up for the operation and at the time of the operation is relatively stable, so that if the child dies the parents have the feeling of having signed the child's death warrant when signing permission for the operation. They know that the child would have survived for a few months at least without the operation, and they know that the operation has eliminated this. They had not seen a child getting more crippled physically or seen their child's head getting larger, or seen the child being less able to walk or pass urine that occur in so many other deformities. The cardiac surgical unit carries an almost unique burden of trust.

One of the saddest comments that comes from parents follows their return to the unit where their child lived and died, whether it be for a heart deformity or leukaemia. They go into the ward where their child was being looked after and see another child in the same bed. They cannot but see that child as a replacement 'love and interest' object for the doctors and nurses, whereas they the parents have no such replacement. If they see the doctors on ward rounds, the death of their own child strikes them much harder with the realisation that the interest and activity of the unit staff has moved on while the parents are still left with their own grief and loss.

With deaths of children with congenital deformities, particularly deaths when they occur in distant special units after weeks of illness, we have a 'dislocation of grief' situation. This occurs most classically in babies who are born prematurely and die several weeks later. When a child dies far away from the home and takes several weeks to die, the parental and the family grief gets out of step. Quite frequently when things go wrong and death is likely, the extended family accept the inevitability of the death and commence their grieving, while the parents who are visiting in the special unit are affected by the optimism of the nurses and are still communicating with the living child. When the child dies later and may or may not be brought home for funeral, the inlaws, grandparents, etc have gone through the initial shock and anger stage of death and are less tolerant of the parents in their grief. The dislocation of grief and affection is a major problem. It is a particular problem in the provinces when children are referred to very specialist units in London. The nurses of these units have spent a vast amount of time and energy on nursing children who later die, and they too need to go through a bereavement process with each child's death if they are to remain healthy. Good units develop their own support system for such cases. Often there is a dedicated padre who helps the parents in their grief and helps the nursing staff in theirs, and the nursing staff and the parents both attend the child's funeral in the institution where the child dies. The child may even be buried in the special unit area and not go back to its home base. This is fine for the unit but when those parents now go home they are in a completely different situation. They have lost both their child and their immediate home support.

The egocentricity of specialist centre workers can be intriguing! Recently at a meeting I listened to some erudite discussions on the technology in diagnosis and surgery of a particular type of congenital deformity of the heart where one hospital series was compared with the other. Neither series was a total community series and both were 'of unit' results but referred to total survival figures with most of the time at home. The family background and home support mechanisms for the children were in no way comparable. They were in different countries in which primary care systems were different. One country has about a half of the postnatal infant mortality rate and cot death rate than the other. In these two operation series no home care aspects were investigated. It was accepted that the mortality rate in the unit from the country with the lower infant and cot death rate was due to the surgical treatment. The surgeons are in a dilemma: they have almost absolute power in their theatres but almost none in homes in far away

Archives of Disease in Childhood, 1989, **64,** 155–158

Joint work in paediatrics: a child psychiatry perspective

J C STURGE

Department of Child Psychiatry, Northwick Park Hospital, Harrow

Child Psychiatry (as one of the 'Cinderella' specialities) has had to look carefully at its interface with other disciplines and at the management of the referral stage of cases. Because so much of our work is in liaison with others, failure to clarify the expectation of the referral, the degree of collaboration needed and who is taking responsibility for what, results in dissatisfactions and misunderstandings for the referrer.

This paper is written in the hope that some of this 'thinking through' that we have undertaken might be helpful to paediatricians making tertiary referrals. First, practices in child psychiatry are considered and then possible implications in paediatrics considered.

Practices in child psychiatry

Several types of response can be offered to referrals to child psychiatric teams. These are:

- An opinion or assessment
- Consultations
- Joint work
- Parallel work
- Handovers

AN OPINION

This is self evident. A referrer asks for an opinion, for example whether a 9 year old boy who keeps hearing his grandfather's voice talking to him is psychotic. Total responsibility remains with the referrer.

A CONSULTATION

A social worker brings a family to see us. Together with the family the problem is presented, for example those consulting want our advice on how to manage an adolescent's violence. They have worked on the problem and feel stuck. Taking the views of both the social worker and the family into account we make an intervention—jargon for a carefully worded statement designed to change the entrenched situation. Those consulting us can reject or accept our view.

JOINT WORK

An education social worker (known as an education welfare officer in some areas) refers a family asking to work jointly with us in getting a school refuser back into school. A social worker refers a family for joint work where there has been intrafamilial sexual abuse. The aim is to work with the family and effect sufficient change for the perpetrator to be reintegrated into the family. Responsibility for the work effecting change is joint: the statutory responsibility in the second example for protecting the child remains with social services.

PARALLEL WORK

A social worker refers a 4 year old child for help with his encopresis. She is meanwhile working with the family on parenting skills. The two agencies take responsibility for different areas of work. They are not independent of each other, however, and this is the least successful model of working.

HANDOVER

Again self explanatory. An educational psychologist refers a family saying the family is complaining of problems that are entirely home and not school related. The referrer plays no further role.

In all these examples responsibility for primary care of course remains with the general practitioner who is kept informed.

Child psychiatric joint work and liaison work with paediatrics

Using the same models, the following are established at the point of referral (see table for examples):

- Expectation of the referral
- Degree of collaboration needed
- Areas of responsibility

Table *Examples of joint work and liaison work between child psychiatry and paediatrics*

Type of problem	*Type of referral*	*Areas of responsibility for child psychiatry*	*Area of responsibility for paediatrics*	*Collaborative or joint aspects*	*Expectation of referral/comment*
Anorexia nervosa	Parallel work	Work on family relationships relevant to the eating problems	Monitoring of physical well being, weight, and metabolic functioning	Agreement of lower weight limit below which child is admitted. This frees child psychiatrist from manipulative weight negotiations with family	Normal eating Weight within normal limits
Overdose	Parallel work	Crisis work with family identifying problems and enabling family to change so as to keep child safe	Medical management of overdose	Joint decision on timing of discharge	Prevention of further overdose
Severe asthma poorly controlled	Parallel work	'Tension-reducing' work with family. Work about anger and resentment around illness	Management of underlying disease	To look at treatment compliance and effect knowledge of family dynamics may have on management	To ascertain if psychiatric intervention could result in stabilising of symptoms, reduction in medication or avoidance of more dramatic medical measures
Physical symptoms with no identifiable physical cause (for example, pain, limps)	Early management: opinion of consultation	For assessment only—formulation of relevance of emotional and family factors	Ongoing management and work towards family recognising what the origin of problem may be	Joint discussion to decide on approach to problem	To aid in assessment of the problem and its management
	Later management: joint work	To help family look at emotional aspects	To respond to family's fears about physical cause of problems	Discussion to enable close cooperation in joint work	Eventual 'handover' to child psychiatrist
Child sexual abuse	Opinion/assessment	For opinion/assessment only. ('Investigate interviews'.) Child psychiatric team only involved in particular circumstances	Medical assessment and examination	Joint decision whether: (1) To contact social services if not yet involved (2) If social services are involved, for planning with social services and police	To complement the medical examination in making a full assessment

GENERAL COMMENTS

While much of the work is in parallel, the joint collaborative role is of great importance to the successful management of *all* these problems.

HANDOVERS

The only clearcut case for handovers is when the paediatricians see what turns out to be an inappropriate referral—for example, a general practitioner refers what purports to be a vomitting problem. On assessment this is clearly a case of bulaemia, that is, self induced vomiting.

More commonly paediatricians seek to hand over cases where they consider the origin of a physical symptom to be psychogenic. Rarely, however, has the family reached this point early in the management of the problem and handover to the child psychiatrists can be counter productive when the family attends 'under duress', still convinced the doctors have simply not investigated fully enough. When families are beginning to look at the possibility of emotional factors joint work can be useful so that the 'expert' on the physical aspects is present to help deal with family's need to somatise problems.

Additionally, we all, of course, have anecdotes of referrals of this type, where later a serious physical condition is identified.

CONSULTATIONS

Paediatricians rarely use this direct face to face form of seeking an opinion in conjunction with the family. It can often reduce the family's resistance to being 'delivered' to the child psychiatric team and expelled from the paediatric arena. A disadvantage is that it is time consuming—the child psychiatrist needs to make an assessment of the family in order to comment.

Some observations on tertiary referrals in paediatrics: 'shared care'

Difficult situations seem too often to arise with this type of referral. The commonest example of this is where the tertiary centre takes over the 'expert' management of the problem while the secondary centre (referring paediatrician) is expected to provide emergency cover or ongoing day to day care. This can result in:

(1) Problems in management of the acute situations because the parents lack faith in the local service and undermine necessary changes in treatment.
(2) Liaison with local services—for example, schools, physiotherapists, etc—not being as coordinated as it should be.

The reasons for the problems are usually:

(1) Failure to clarify at the point of referral the model of shared care being sought.
(2) Failure to clarify discrete areas of responsibility and, in particular, failure to make clear to the family who is responsible for what.
(3) Geographical distance between the two centres making close collaboration difficult.

To avoid this problem referrals to tertiary centres should be understood by all those involved (referrer, family and tertiary centre) and be for one of the following reasons:

(1) For opinion and advice only (responsibility remains with referring paediatrician).
(2) For takeover of care for an agreed period with responsibility passing back to the referrer at the end of this time.
(3) For a long term handover of care when tertiary centre takes over responsibility, liaising with the general practitioner.
(4) For consultations.

Joint clinics are becoming more widely available and offer an excellent opportunity for close collaboration and clear definition of roles and responsibilities.

In my view this could be improved still further by using a model closer to that described in child psychiatry where consultations are offered. It would be clearer to the family that the referring paediatrician and they themselves were seeking the consultation if the referring paediatrician were to fetch them in and then sit with the family (and not with the 'specialist') and jointly consult. At the end there should be an opportunity for the referring paediatrician and family to discuss, in the absence of the 'specialist', their reaction to the opinion given and whether or not they (family and referring paediatrician) want to act on the advice given. This makes very clear the nature of the referral—that responsibility remains with the referring paediatrician—and can enhance relationships by fully involving the family.

Shared care: a misnomer

The term shared or joint care when the term used is in relation to a paediatrician referring to an expert at another centre is usually a misnomer: it is not the overall care that is shared but other aspects of management. Central responsibility cannot be shared where those trying to share it do not work alongside and are not in frequent contact within the same establishment. The situation is analogous to divorced parents. Joint care and control can only work where parents are living together. Judges and the courts are now clear that joint care and control are not in the best interests of the child but that for continuity and sense of security, care and control should be with one parent only and with the parent most frequently in contact with the child. Joint custody is sometimes granted (though less and less so), and extending the analogy, this would mean that the local paediatrician (parent with care and control) would consult with the 'specialist' (parent with access only) over major decisions (joint custody issues).

Correspondence to Dr JC Sturge, Department of Child Psychiatry, Northwick Park Hospital, Watford Road, Harrow, Middlesex HA1 3UJ.

Archives of Disease in Childhood, 1989, **64,** 159–165

Personal practice

The investigation of haematuria

R H R WHITE

Department of Nephrology, The Children's Hospital, Birmingham

Visible haematuria is a common presenting symptom of renal and urinary tract disease in children, and is often recurrent. Symptomless microscopic haematuria is not frequently detected on routine examination of the urine during coincidental illness or population screening.[1 2] Most cases are found to be caused by primary glomerular disorders; however, surgically remediable causes are occasionally diagnosed, and it is mandatory that every child is appropriately investigated. Such an assessment should be tailored to the individual patient's particular circumstances and not carried out in a routine and perhaps needlessly invasive manner. It is best to proceed in planned steps, aimed first at confirming the presence of haematuria, then establishing the anatomical site of bleeding, and finally the diagnosis. A logical plan requires a knowledge of the causes, which are reviewed below.

Non-glomerular causes (table 1)

Bleeding from the genitalia, as in severe vulvovaginitis, gross sexual abuse, or vaginal foreign body may present with apparent haematuria, and careful inspection of the genitalia is an essential procedure. For the first menstrual period to be mistaken for haematuria is something which I have observed only once in more than 25 years. Bleeding from an anal fissure into a baby's nappy, where it may be diffused by urine, is a rare cause of difficulty.

Table 1 *Non-glomerular causes of haematuria*

Non-glomerular causes of haematuria
Genital or anal bleeding
Urinary tract infection
Hypercalciuria
Calculus
Hydronephrosis
Neoplasm
Trauma
Schistosoma haematobium infection
Subacute bacterial endocarditis
Sickle cell disease
Tuberculosis
Renal cysts
Loin pain-haematuria syndrome
Blood coagulation disorder

Acute urinary tract infection may be accompanied by microscopic haematuria, but a clinical presentation with visible haematuria is unusual in children. Hypercalciuria has recently been reported as an occasional cause of persistent microscopic haematuria,[3] and its correction by a liberal fluid intake together with the avoidance of a high dietary calcium intake or, if necessary, the use of diuretics, is usually curative.

Surgically remediable causes of haematuria include calculus, hydronephrosis, neoplasm, and trauma, and a suitable imaging procedure must be undertaken to exclude them. Causes of haematuria in the bladder are very rare during childhood, and cystoscopy is, almost without exception, a needless investigation.[4 5] The ease of international travel means that today, however, some children living in temperate countries may previously have resided in tropical zones where the parasite *Schistosoma haematobium* is prevalent. Prompt treatment of schistosomiasis is essential if hydronephrosis due to fibrotic changes at the ureterovesical junction are to be avoided.[6]

Other infrequent causes of haematuria include subacute bacterial endocarditis, sickle cell disease, tuberculosis, and renal cysts. Although adult polycystic disease is, today, increasingly diagnosed in childhood by ultrasound screening, haematuria rarely occurs before adulthood. The loin pain-haematuria syndrome, well described in young women,[7] is rare in childhood; I have seen only two cases–a 15 year old girl and a 12 year old boy. The diagnosis eludes conventional imaging procedures and renal angiography is necessary in suspected cases. Haematuria may occasionally follow unusually strenuous and sustained exertion, usually in young adult males, although I have once seen it in a healthy 12 year old boy. Although urinary tract bleeding may complicate coagulation disorders, haematuria is almost never the presenting symptom.

Glomerular causes (table 2)

PROLIFERATIVE GLOMERULONEPHRITIS

In typical poststreptococcal glomerulonephritis of moderate severity, signs of salt and water retention are present, with hypertension, raised jugular venous pressure, clinical or radiological cardiomegaly, and minimal oedema. In mild cases, however, these features may be absent. The condition can only be diagnosed with confidence within one or two months of onset of haematuria, when the serum titres of streptococcal antibodies are raised and the serum complement C3 component is reduced but gradually returning to normal. Poststreptococcal nephritis is not a recurrent disorder, even though in severe cases it may be slow to heal, and the diagnosis need not be seriously entertained in a child who has had repeated attacks of macroscopic haematuria over a period of six months or more.

Although a nephrotic or nephritic presentation is the rule in mesangiocapillary glomerulonephritis, Cameron *et al* noted haematuria as the first symptom in 7% of cases.[8] Persistent, heavy proteinuria is almost invariably present, however, and a low serum C3 concentration would be strongly suggestive while a normal concentration would not exclude the condition.[9] Haematuria is the commonest renal manifestation of Henoch-Schönlein purpura.[10] While recognition of the systemic features will obviate any diagnostic difficulty in the vast majority of cases, an occasional patient may present with symptomless haematuria months or even years after the initial illness has resolved; the diagnosis is then dependent on a careful history. This clinical pattern is of interest because of its similarity to that of IgA nephropathy, and the occurrence of mesangial IgA deposits in Henoch-Schönlein nephritis, together with a report of twin boys, one affected by Henoch-Schönlein nephritis and the other by IgA nephropathy,[11] suggests that the two conditions may have a common immunopathological basis.

IGA NEPHROPATHY

IgA nephropathy is probably the commonest cause of recurrent, symptomless, macroscopic haematuria and persistent microscopic haematuria in children and young adults. Since its first description in 1968[12] a wealth of literature has been published and the subject is well reviewed by D'Amico.[13] There is appreciable geographical variation in its incidence; it is commoner in southern than north western Europe and is particularly common in Japan and South East Asia. Estimates of its incidence will vary according to referral practice; since the screening of Japanese school children for urinary abnormalities was begun in 1974, IgA nephropathy has been the commonest form of primary glomerulopathy to be diagnosed in paediatric renal units.[2] A low incidence has been reported in negroes; some workers have reported a significant association with HLA-DR4 antigens but others have failed to confirm this, and there are rare reports of siblings being affected.[2]

Table 2 *Main glomerular causes of haematuria*

Proliferative glomerulonephritis:
  Acute poststreptococcal
  Mesangiocapillary
  Henoch-Schönlein
IgA nephropathy
Alport nephropathy and variants
Thin membrane disease
Minor glomerular abnormalities

The light microscopic findings in renal biopsy specimens in children are generally minimal or consist of mild, focal, and segmental mesangial proliferation. A minority of children who have accompanying persistent proteinuria may later develop segmental glomerular sclerosis. The diagnosis is established by the finding, on immunofluorescence microscopy, of diffuse mesangial deposits of IgA, occasionally in isolation but more usually with IgG or C3, or both. On electron microscopy, dense deposits corresponding to these immune complexes are observed particularly in the perimesangial regions. The aetiology remains uncertain and it is still debated whether the mesangial deposits represent increased production and delivery or decreased clearance of IgA immune complexes.[2] An interesting recent finding is the presence in a few patients of circulating antigliadin antibodies, coupled with flat mucosa on jejunal biopsy and clearance of haematuria in response to a gluten free diet,[14] suggesting a possible connection between the relatively high prevalance of IgA nephropathy in Italy and the use of wheat based pasta as the staple diet.

The course of the illness is generally protracted, although not as often progressive as it is in adults. About one third of children lose their symptoms, but the remainder continue to have haematuria, if only microscopic, and no effective treatment has yet been found. A few children develop proteinuria, associated with segmental glomerular sclerosis, and are at risk of future chronic renal failure.[2] IgA deposition is reported to recur in renal transplants, although the clinical manifestations are mild and renal function remains stable in the short term.[15]

THE ALPORT NEPHROPATHY

The next most common cause of glomerular haematuria in childhood is the Alport nephropathy. The term Alport's syndrome should perhaps be confined to those families in which neurosensory deafness occurs in addition to nephritis, as originally described.[16] Males more often exhibit deafness than females, and typically progress to chronic renal failure in early adulthood, whereas most females remain in apparently good health throughout life. In a few families deafness is absent, even in males, who survive to a greater age before developing chronic renal failure; these we have referred to as Alport variants.[17] A variety of ocular defects have also been described[18 19]; these include posterior polymorphous dystrophy of the cornea, anterior lenticonus, and perimacular flecks, all of which represent basement membrane defects. We have observed strong positive correlation between deafness, ocular abnormalities, proteinuria, and chronic renal failure.[19 20]

Like IgA nephropathy, the Alport nephropathy is of geographically variable prevalence. This may reflect true racial differences, referral practices, and the morphological criteria used for diagnosis. The condition is diagnosed in specimens from renal biopsies undertaken in children with haematuria more than twice as frequently in Birmingham than in Manchester and Leeds,[21 22] although the incidence of IgA nephropathy in all three centres is similar. The lack of reports of hereditary nephritis from Singapore suggest that it is uncommon in the Chinese, although we have diagnosed it in one such family in Birmingham. I have not yet seen it in a negro child and know of no published reports of its occurrence.

The inheritance of the Alport nephropathy may be heterogeneous, although most of the published pedigrees[23] and all that we have studied in Birmingham[20] are consistent with X linkage. It requires male to male inheritance to disprove X linked inheritance, and such instances are not only rare but also unsubstantiated by unequivocal ultrastructural diagnostic criteria. A family history of nephritis and deafness is not always obtained as female 'carriers' may have asymptomatic microscopic haematuria as their only clinical manifestation. It is therefore essential to test the urine of all first degree relatives of children presenting with haematuria before dismissing the disorder as nonfamilial; we have detected at least 10 affected families in this manner.[21] Even then, haematuria in females may be intermittent, and a single negative test does not exclude the diagnosis.[20] It is uncertain whether those rare cases diagnosed on firm morphological grounds in the absence of affected relatives are true mutants or the offspring of affected women who do not display clinical manifestations.[17] The genetics of the Alport nephropathy will ultimately be settled by means of DNA probes, and preliminary studies point strongly towards an abnormal gene on the X chromosome.[24]

The changes seen on light microscopy of renal biopsy specimens are non-specific; segmental glomerulosclerosis and interstitial foam cells are not usually found in young children but develop as a prelude to declining renal function and correlate strongly with the presence of heavy proteinuria.[17] Immunofluorescence is essentially negative. The hallmark of diagnosis lies in the characteristic ultrastructural alterations of the glomerular basement membrane.[25–27] This consists of irregular thickening of the membrane, with complex replication of the lamina densa, the clear spaces between the layers containing electron dense aggregates, and has been likened to a basket weave.[28] Although we have observed similar but strictly localised changes in a variety of other glomerulopathies, widespread glomerular basement membrane involvement is diagnostic of the Alport nephropathy.[28] That this abnormality may be due to defective biochemical composition[29] is supported by the absence from the glomerular basement membrane of the Goodpasture antigen.[30]

'THIN MEMBRANE DISEASE'–AN ALPORT VARIANT?

In addition to thickening of the glomerular basement membrane attenuated segments may be seen.[17] Occasionally they are so thin that the lamina densa becomes interrupted. Bernstein has suggested that this may be the primary lesion,[31] and the observation by Habib *et al* that this is the prevalent abnormality in younger children lends support to this concept.[29] In some children with familial haematuria there is diffuse attenuation of the glomerular basement membrane.[17] When originally described this was believed to be a benign condition,[32] and this appears to be true in many cases. Chronic renal failure of late onset has, however, since been reported in relatives of four patients with thin membrane disease.[29] I have recently biopsied two siblings with haematuria, the older of whom had classical changes of the glomerular basement membrane and the younger, a boy aged 18 months, diffuse attenuation only. Similar ultrastructural differences were reported in a mother and son, respectively, by Habib *et al.*[29]

The relationship between thin membrane disease and the Alport nephropathy is a complex one and requires further evaluation. We are currently undertaking morphometric measurements in an attempt to elucidate this problem, having first determined what we believe to be the normal range of thickness in the glomerular basement membrane in children with minimal change nephrotic syndrome.[33] In the meantime, a cautious prognosis must be given in children with familial haematuria who show thin membrane disease on renal biopsy.

MINOR GLOMERULAR ABNORMALITIES

A few children with persistent haematuria, in whom comprehensive investigation is normal, show little or no abnormality on renal biopsy, and appear to run a benign course. The reason for the haematuria remains unexplained. A few biopsy specimens show bright, immunofluorescent C3 staining of arterioles,[34] the significance of which is uncertain. Like Habib *et al*,[29] however, we have also observed an ultrastructurally normal glomerular basement membrane in three children representing families with clinically typical Alport's syndrome.[28] One child has subsequently developed characteristic changes of the membrane in a repeat biopsy specimen, and clearly a normal result on biopsy in the presence of familial nephritis cannot necessarily be considered benign.

A management plan (table 3)

HISTORY AND PHYSICAL EXAMINATION

History taking should be directed towards symptoms such as frequency, dysuria, and loin pain: joint pains and rash; deafness in the child or family; a family history of renal disease; racial and geographical factors; and the possibility of exposure to tropical disorders. A note should be made of the child's age; haematuria beginning before 5 years of age is more likely to be caused by hereditary nephritis than IgA nephropathy. A complete physical examination must always be performed; points requiring particularly attention are the presence of oedema, hypertension, raised jugular venous pressure, bruising or petechiae, joint swelling, renal masses, anal and genital inflammation, trauma, or bleeding. Any suggestion of deafness, from the history or examination, will require an audiogram for confirmation.

Table 3 *An initial managment checklist*

Procedure	*Possible findings*
History taking	Frequency and dysuria
	Loin pains, renal colic
	Joint pains, rash
	Bleeding tendency
	Deafness
	Family history
	Strenuous exertion
	Tropical exposure
Examination	Oedema
	Hypertension
	Raised jugular venous pressure
	Purpura, joint swelling
	Renal mass
	Genital or anal bleeding
	Deafness
Urine examination	Pyuria, bacteriuria
	Granular casts
	Dysmorphic erythrocytes
	Schistosoma haematobium
	Proteinuria
	Hypercalciuria
Imaging	Gross lesions

URINE EXAMINATION

The initial task is to confirm the presence of haematuria, which is not invariably the cause of suggestive discoloration of the urine. For example, uric acid crystals deposited in a baby's nappy impart a faint, pink tinge, which may be misinterpreted by a naturally anxious mother. Certain pigments, such as those contained in beetroot and eosin used in boiled sweets, are said to cause red discoloration in certain individuals; rifampicin causes a bright orange colour which could be mistaken by the unwary. Haemoglobinuria is rarely seen in white children, when it may be caused by cold agglutinins complicating mycoplasma pneumonia; it is an occasional complication of glucose-6-phosphate dehydrogenase deficiency in negroes living in regions where malaria caused by *Plasmodium falciparum* is prevalent.

Macroscopic haematuria imparts a characteristically smoky appearance to the urine; microscopic haematuria produces no change visible to the naked eye. Positive results from chemical strip tests (Hemastix, Labstix, etc) rely on haemolysis due to extremes of pH and osmolar change in the urine. Trace positive readings often occur in healthy subjects while ambulant, in the absence of haematuria detectable by microscopy, and I have occasionally observed negative results in association with minimal microscopic haematuria. It is therefore necessary to confirm the presence of haematuria by microscopy, and an inexpensive microscope should be regarded as an essential item of equipment for a renal clinic. It is also preferable, incidentally, to hold a renal clinic in the morning when the cellular (and bacterial) content of the urine is less likely to be influenced by dilution, and an early morning specimen collected by the patient at home for protein determination is still reasonably fresh.

Examination of the urine offers the opportunity to look for other abnormalities which may give a clue to the aetiology of the haematuria. Bacteriuria may be observed microscopically,[35] but infection must be excluded by routine urine culture. A glomerular origin would be supported by the presence in the urine of granular casts. Erythrocytes which have passed through the glomerular capillary wall become misshapen and show appreciable variation in diameter. Birch *et al* reported that glomerular and lower tract haematuria could be reliably distinguished by phase contrast microscopy.[36] I have not personally employed this technique, but long experience with conventional microscopy has taught me to recognise dysmorphic erythrocytes with reasonable confidence. Where there is a history of tropical exposure, centrifuged urine should be examined microscopically for the ova of *Schistosoma haematobium*, which are recognised by the terminal spine.

While heavy haematuria of either upper or lower tract origin will be accompanied by some proteinuria, persistent heavy proteinuria is virtually diagnostic of glomerular pathology. To eliminate postural and exercise effects, it is essential to measure proteinuria only in urine secreted by the kidneys during recumbency. This may take the form of a timed, overnight collection in which the proteinuria is expressed as mg/hour/m^2 body surface area, but is liable to error in small or enuretic children, and we found an excellent correlation with the protein:creatinine ratio measured in an early morning urine sample.[37] The upper limit of normal, based on 377 healthy individuals aged 3–19 years, is 20 mg:mmol. The same early morning urine can be used to determine the calcium:creatinine ratio, which should be <0·7 mmol:mmol, and this should be done routinely in children with unexplained haematuria.

IMAGING

The former practice of performing intravenous urography on children with unexplained haematuria has been superseded by real time ultrasonography that is capable of detecting all gross lesions equally well and some, such as renal cysts or a non-functioning hydronephrotic kidney, more effectively. It should be combined with a plain abdominal radiograph, however, as a small, radio-opaque calculus in the ureter may escape detection. Children who show clearcut nephritic signs, as already outlined, and have proteinuria and granular casts in addition to haematuria, can be investigated as cases of presumed glomerulonephritis without the need for preliminary imaging. Cystoscopy and retrograde urography are rarely indicated in children with isolated haematuria, who are best referred to a nephrologist rather than a urologist.

THE ROLE OF RENAL BIOPSY

In practice most children presenting with haematuria prove to have negative initial screening procedures as outline above, and the findings point towards a glomerular origin. The final step in diagnosis is the further evaluation of glomerulonephritis, in which renal biopsy plays a major part. This is an invasive procedure, however, which should not be undertaken lightly. Some children can be adequately managed without biopsy, and the figure shows a scheme for assessing its need.

Patients who show heavy proteinuria in addition to haematuria are likely to have some kind of proliferative glomerulonephritis and should be investigated promptly. In poststreptococcal nephritis the serum antistreptolysin titre is not always raised, and it is essential also to measure the anti-DNase B titre. The serum C3 is usually depressed but returns to normal within eight weeks; therefore, if the initial concentration is reduced, the measurement must be repeated after four to eight weeks, for confirmation. A persistently low concentration, usually together with persisting, heavy proteinuria, would be strongly suggestive of mesangiocapillary glomerulonephritis,[8, 9] and renal biopsy would be indicated.

A decision is reached with somewhat greater difficulty in children whose proteinuria is minimal or absent, who in fact account for most patients presenting with haematuria. It cannot, unfortunately, be argued that the condition is necessarily benign, for the Alport nephropathy is rarely associated with heavy proteinuria before 10 years of age in boys, and much later in girls.[17] On the other hand, as there is no effective treatment for either Alport's syndrome or IgA nephropathy, diagnosis is not a matter of urgency. My practice is to instruct the mother to test early morning urine samples for blood every two weeks for a period of six months, using Hemastix strips, and record the results. At the same time she is asked to test urine from all first degree relatives, avoiding the menstrual periods in adult women.

If tests on the child show more or less continuous microscopic haematuria, or if family testing is positive, renal biopsy should now be arranged. If, on the other hand, family testing is negative and the child's haematuria is intermittent, a decision may be reached to defer biopsy, and the parents can be reassured with reasonable confidence that a serious underlying disorder is unlikely. Unlike proteinuria and purely microscopic haematuria, visible haematuria is apt to cause the parents considerable anxiety, and in these circumstances biopsy may be warranted in order to increase the paediatrician's confidence in reassuring them.

Finally, to attain a high success rate combined with low risks, the performance of renal biopsy requires initial training and continuing experience, which are best obtained in a centre with a turnover of about 50 biopsies a year. In the past I have many

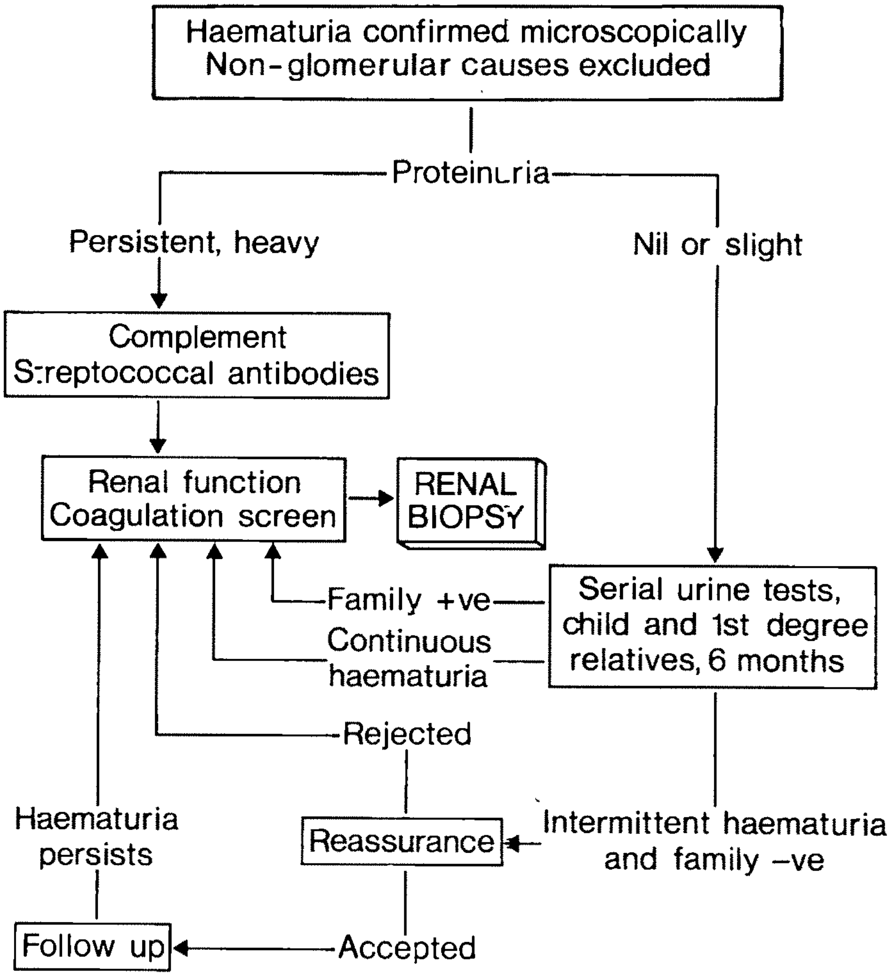


Figure *A scheme for the selection of children with haematuria for renal biopsy.*

times had to repeat biopsies carried out by enthusiastic but inexperienced 'handymen', and it is my policy not to teach the technique to paediatric trainees unless they are committed to a career in paediatric nephrology. The same principles apply to the processing and histological interpretation of specimens. It should be borne in mind that IgA nephropathy requires immunofluorescence and the Alport nephropathy electron microscopy to establish the diagnosis; in the early stages they are indistinguishable by light microscopy alone. I would therefore regard it as unethical, today, for biopsy to be performed in any circumstances where the appropriate expertise and facilities do not exist. In the United Kingdom most (but still not all) biopsies are now performed by trained paediatric nephrologists working in hospitals affiliated to medical schools, and these are the appropriate points of referral for children with haematuria. Moreover, if we are to continue extending our knowledge of the natural history of these still poorly understood disorders, the collaboration of skilled adult nephrologists in the ongoing care of young adult patients is equally desirable.

This article is based on a lecture given to the Philippine Society of Nephrology on 25 March 1988, and is reproduced (modified) by courtesy of *The Philippine Journal of Nephrology*.

References

[1] Meadow SR, White RHR, Johnston NM. Prevalence of symptomless urinary tract disease in Birmingham schoolchildren. I-Pyuria and bacteriuria. *Br Med J* 1969;iii:81–4.
[2] Yoshikawa N, Ito H, Yoshiara S, Nakahara C, Yoshiya K,

Hasegawa O. Clinical course of immunoglobulin A nephropathy in children. *J Pediatr* 1987;**110:**555–60.

[3] Stapleton FB, Roy S, Noe HN, Jerkins G. Hypercalciuria in children with hematuria. *N Engl J Med* 1984;**310:**1345–8.

[4] Glasgow EF, Moncrieff MW, White RHR. Symptomless haematuria in childhood. *Br Med J* 1970;**ii:**687–92.

[5] Bullock N. Asymptomatic microscopical haematuria. *Br Med J* 1986;**292:**645.

[6] Gelfand M. Shistosomiasis. In: Jelliffe DB, Stanfield JP, eds. *Diseases of children in the subtropics and tropics*. 3rd ed. London: Arnold, 1978:883–914.

[7] Little PJ, Sloper JS, de Wardener HE. A syndrome of loin pain and haematuria associated with disease of peripheral renal arteries. *Q J Med* 1967;**36:**253–9.

[8] Cameron JS, Ogg CS, Turner DR, *et al.* Mesangiocapillary glomerulonephritis and persistent hypocomplementaemia. In: Kincaid-Smith P, Mathews TH, Becker EL, eds. *Glomerulonephritis*. New York: Wiley, 1973:541–56.

[9] Cameron JS, Ogg CS, White RHR, Glasgow EF. The clinical features and prognosis of patients with normocomplementaemic mesangiocapillary glomerulonephritis. *Clin Nephrol* 1973;**1:** 8–13.

[10] Meadow SR, Glasgow EF, White RHR, Moncrieff MW, Cameron JS, Ogg CS. Schölein-Henoch nephritis. *Q J Med* 1972;**41:**241–58.

[11] Meadow SR, Scott DG. Berger disease: Henoch-Schönlein syndrome without the rash. *J Pediatr* 1985;**106:**27–32.

[12] Berger J, Hinglais N. Les dépôts intercapillaires d'IgA-IgG. *Journal d'Urologie et de Nephrologie* 1968;**74:**694–5.

[13] D'Amico G. Idiopathic IgA mesangial nephropathy (editorial). *Nephron* 1985;**41:**1–13.

[14] Fornasieri A, Sinico RA, Maldifassi P, Bernasconi P, Vegni M, D'Amico G. IgA-antigliadin antibodies in IgA mesangial nephropathy (Berger's disease). *Br Med J* 1987;**295:**78–80.

[15] Berger J, Yaneva H, Nabarra B, Barnabel C. Recurrence of mesangial deposition of IgA after renal transplantation. *Kidney Int* 1975;**7:**232–41.

[16] Alport AC. Hereditary familial congenital haemorrhagic nephritis. *Lancet* 1927;**i:**504–6.

[17] Yoshikawa N, White RHR, Cameron AH. Familial haematuria: clinico-pathological correlations. *Clin Nephrol* 1982;**17:**172–82.

[18] Govan JAA. Ocular manifestations of Alport's syndrome: a hereditary disorder of basement membranes? *Br J Ophthalmol* 1983;**67:**493–503.

[19] Thompson SM, Deady JP, Willshaw HE, White RHR. Ocular signs in Alport's syndrome. *Eye* 1987;**1:**146–53.

[20] White RHR. The Alport nephropathy. In: Murakami K, Kitagawa T, Yabuta K, Sakai T, eds. *Recent advances in nephrology*. Proceedings of the 7th International Congress of Paediatric Nephrology, 1986. Amsterdam: Elsevier, 1987: 201–6.

[21] White RHR. Asymptomatic microscopical haematuria. *Br Med J* 1986;**292:**1599.

[22] Miller PFW, Spiers NI, Aparicio SR, *et al.* Long-term prognosis of recurrent haematuria. *Arch Dis Child* 1985;**60:**420–5.

[23] Feingold J, Bois E, Chompret A, Broyer M, Gubler M-C, Grunfeld J-P. Genetic heterogeneity of Alport syndrome. *Kidney Int* 1985;**27:**672–7.

[24] Flinter FA, Bobrow M, Chantler C. Alport's syndrome or hereditary nephritis. *Pediatric Nephrology* 1987;**1:**438–40.

[25] Hinglais N, Grunfeld J-P, Bois E. Characteristic ultrastructural lesion of the glomerular basement membrane in progressive hereditary nephritis (Alport's syndrome). *Lab Invest* 1972;**27:**473–87.

[26] Spear GS, Slusser RJ. Alport's syndrome; emphasizing electron microscopic studies of the glomerulus. *Am J Pathol* 1972;**69:**213–24.

[27] Churg J, Sherman RL. Pathologic characteristics of hereditary nephritis. *Arch Pathol Lab Med* 1973;**95:**374–9.

[28] Yoshikawa N, Cameron AH, White RHR. The glomerular basal lamina in hereditary nephritis. *J Pathol* 1981;**135:**199–209.

[29] Habib R, Gubler M-C, Hinglais N, *et al.* Alport's syndrome: experience at Hopital Nêcker. *Kidney Int* 1982;**21:**S20–8.

[30] Savage COS, Pusey CD, Kershaw MJ, *et al.* The Goodpasture antigen in Alport's syndrome: studies with a monoclomal antibody. *Kidney Int* 1986;**30:**107–12.

[31] Bernstein J. Hereditary renal disease. In: *Kidney disease: present status,* International Academy of Pathology monograph No 20. Baltimore: Williams and Wilkins, 1979:295–326.

[32] Rogers PW, Kurtzman NA, Bunn SM Jr, White MG. Familial benign essential hematuria. *Arch Intern Med* 1973;**131:**257–62.

[33] Morita M, White RHR, Raafat F, Barnes JM, Standring DM. Glomerular basement membrane thickness in children: a morphometric study. *Pediatric Nephrology* 1988;**2:**190–5.

[34] Trachtman H, Weiss R, Bennett B, Greifer I. Isolated haematuria in children: indications for a renal biopsy. *Kidney Int* 1984;**25:**94–9.

[35] Robins DG, White RHR, Rogers KB, Osman MS. Urine microscopy as an aid to detection of bacteriuria. *Lancet* 1975;**i:**476–8.

[36] Birch DF, Fairley KF, Whitworth JA, *et al.* Urinary erythrocyte morphology in the diagnosis of glomerular hematuria. *Clin Nephrol* 1983;**20:**78–84.

[37] Elises JS, Griffiths PD, Hocking MD, Taylor CM, White RHR. Simplified quantification of urinary protein excretion in children. *Clin Nephrol* 1988;**30:**225–9.

Correspondence to Professor RHR White, Department of Nephrology, The Children's Hospital, Ladywood Middleway, Birmingham B16 8ET.

Archives of Disease in Childhood, 1989, **64,** 166–171

Regular review

Hearts with one ventricle: current concepts and management

I D SULLIVAN AND J F N TAYLOR

Cardiothoracic Unit, The Hospital for Sick Children, Great Ormond Street, London

Nature of the problem

Many congenital cardiac malformations result in a heart with only one effective ventricle. In most of these there is a second ventricle present, but it is too small to sustain cardiac output making construction of a biventricular circulation impossible. These hearts may be classified according to the atrioventricular connection. There are two possibilities: the atria are each connected to a separate ventricle, or the atria are connected to only one ventricle.

When each of the atria is connected separately to one of two ventricles, either ventricle may be too small. The right ventricular cavity is small in almost all cases of pulmonary atresia with intact ventricular septum, and in some hearts in which the tricuspid valve straddles a ventricular septal defect. A small left ventricular cavity is the hallmark of the hypoplastic left heart syndrome.

When the atria are connected to only one ventricle (irrespective of the possible presence of another rudimentary ventricle) there is a 'un ventricular atrioventricular connection'.[1 2] If both atria are connected to one ventricle, it is termed 'double inlet' ventricle. There are usually two atrioventricular valves under these circumstances but sometimes a common atrioventricular orifice drains both atria. Alternatively, one atrioventricular connection may be absent (fig 1). In tricuspid atresia the right atrioventricular connection is absent. Systemic venous return to the right atrium has an obligatory flow across the atrial septum into the left atrium and together with pulmonary venous blood passes to the left ventricle through the mitral valve. There is obligatory transatrial flow of pulmonary venous blood in the opposite direction (from left atrium to right atrium) in hearts in which the mitral valve is atretic or the left atrioventricular connection absent. A valve is atretic if it is formed but imperforate; the atrioventricular connection is absent if there is no valve tissue at all.

Although these malformations are comparatively rare, tricuspid atresia, double inlet ventricle, and hypoplastic left heart syndrome each accounted for nearly 5% of the total number of symptomatic infants with congenital heart disease in a British survey of the decade preceding 1982.[3] In addition, about a third of those patients with double inlet ventricle will present after infancy (Franklin RCG, Deanfield JE, Anderson RH, *et al*, unpublished observations).

Presentation

The nature of the ventriculoarterial connection and the degree of obstruction to pulmonary or systemic outflow will determine the clinical presentation. Symptoms of heart failure caused by high pulmonary blood flow develop as the pulmonary vascular resistance falls in early infancy if neither pulmonary nor systemic ventricular outflow is obstructed. Obstruction to systemic or pulmonary blood flow is common. The obstruction may occur at the pulmonary or the aortic valve, but more often is the result of subvalvular muscular narrowing, either just below the valve, or less often at a restrictive ventricular septal defect when one great artery arises from a rudimentary ventricle. It is rare for a child to be born with obstruction to both systemic and pulmonary blood flow.

Mild to moderate 'pulmonary stenosis' may regulate pulmonary blood 'appropriately'. The balanced haemodynamic state that results may be compatible with survival into adult life with minimal symptoms. Severe 'pulmonary stenosis' causes low pulmonary blood flow with cyanosis. Hypercyanotic episodes, similar to those classically associated with tetralogy of Fallot, may occur when there is a dynamic element to the subpulmonary obstruction. Under extreme circumstances, in which the pulmonary outflow is atretic at birth, pulmonary blood flow

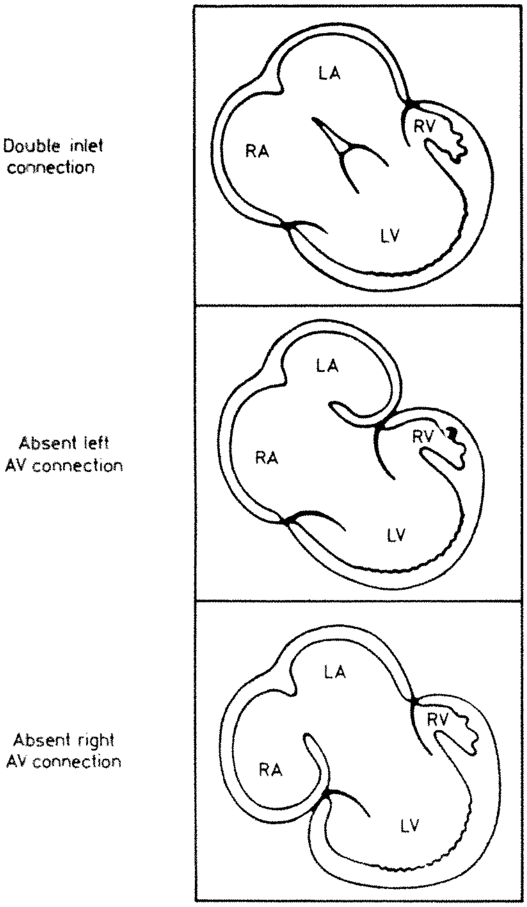


Fig 1 *Simplified diagram of atrioventricular connections that may occur in univentricular atrioventricular connection to a morphological left ventricle. (Adapted by permission of MTP Press Ltd, Lancaster.[1]) AV=atrioventricular; LA=left atrium; LV=left ventricle; RA=right atrium; RV=right ventricle.*

is precarious as it is dependent on the persistence of the ductus arteriosus.

Obstruction to the systemic outflow results in the particularly adverse combination of low systemic blood flow and high pulmonary blood flow; early neonatal heart failure is usually the result. Systemic outflow obstruction in hearts with either a double inlet ventricle or an absent atrioventricular connection occurs typically when the aorta arises from a rudimentary subaortic ventricle. If this is the case, after the duct has closed the total systemic blood flow must pass through the ventricular septal defect and small subaortic chamber, both of which are potential sites for subaortic stenosis (fig 2). The common addition of coarctation of the aorta to the anomaly gives a dismal prognosis with conventional surgical management (Franklin RCG, Deanfield JE, Anderson RH, *et al*, unpublished observations).[4] If there is complete obstruction to systemic outflow from the heart, systemic perfusion will be totally dependent on right to left ductal shunting; this is usual in hypoplastic left heart syndrome. Perfusion of the head and neck vessels together with the coronary arteries becomes reliant on retrograde flow into the hypoplastic ascending aorta from the duct. Ductal closure is, of course, fatal.

Palliative surgery

Most children with double inlet ventricle or tricuspid

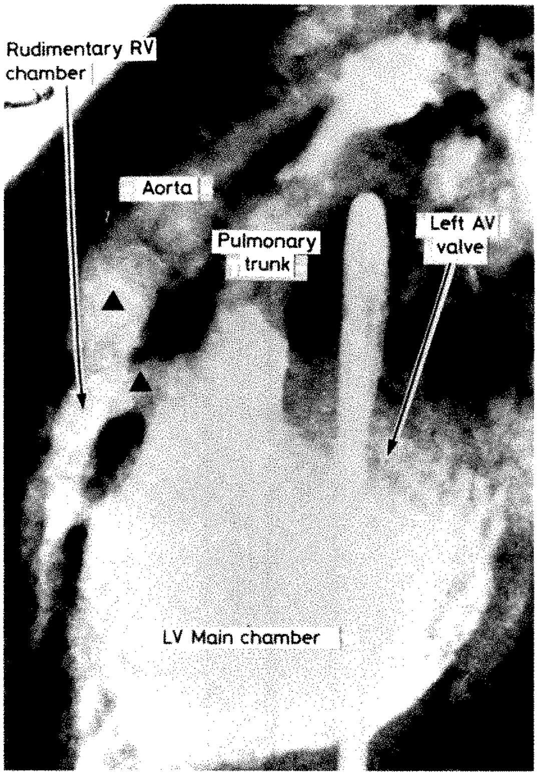


Fig 2 *Lateral angiocardiogram from a patient with absent right atrioventricular connection and ventriculoarterial discordance (tricuspid atresia with transposition of the great arteries). The aorta arises anteriorly from the rudimentary right ventricle. The subaortic infundibulum and the ventricular septal defect (arrowheads), are potential sites for subaortic obstruction. (Adapted with permission from Pediatric Cardiology.[2]) AV=atrioventricular; LV=left ventricle; RV=right ventricle.*

atresia will require palliative surgery in infancy to survive (Franklin RCG, Deanfield JE, Anderson RH, *et al*, unpublished observations).[4] Most commonly this will consist of either a systemic to pulmonary artery shunt to augment inadequate pulmonary blood flow, or a pulmonary artery band to diminish excessive pulmonary blood flow. Although palliative surgery may ensure immediate survival, about half of those with tricuspid atresia die by the age of 5 years, and two thirds by the age of 20 years.[5] The rate of survival after palliative surgery for double inlet ventricle is similar (Franklin RCG, Deanfield JE, Anderson RH, *et al*, unpublished observations). Consequently, definitive surgery will be required for these patients to survive childhood.

Definitive surgery: the Fontan circulation

In a few exceptional cases with specific anatomy surgical septation of the ventricle may be possible, thus creating a biventricular circulation. Definitive surgery applicable to a wider group of hearts with one ventricle was first performed by Fontan's group.[6] This novel surgical approach has revolutionised management. It established the feasibility of connecting the pulmonary and systemic circulations in series with only one—the systemic—ventricle (fig 3). This is achieved by connecting the systemic venous return directly to the pulmonary arterial circuit.

How can the solitary ventricle power both systemic and pulmonary circulations in series? The physiology underlying the Fontan circulation has been described in lucid yet comparatively simple terms by Bull.[7] In a normally connected heart, if the left ventricle becomes progressively smaller, the left ventricular end diastolic pressure rises, as does the left atrial and pulmonary venous pressure; the eventual consequence is pulmonary oedema. In contrast, if the right ventricle becomes progressively smaller, the right ventricular end diastolic pressure rises as does right atrial pressure. Eventually (provided pulmonary vascular resistance is low) right atrial pressure will exceed pulmonary artery pressure, and may be transmitted directly. This assumes that the right ventricle serves as a passive conduit and does not cause obstruction to flow. Blood may then flow from the right atrium to the pulmonary artery without any augmentation of flow from the right ventricle. Under these circumstances the circulation may be maintained 'without' the right ventricle at the expense of a high systemic venous pressure. The maintenance of a low systemic venous pressure is the function of the right ventricle under normal circumstances.

The same concept permits the circulation to 'work' when systemic venous return is connected directly to the pulmonary arteries in the absence of a right ventricle. Specific criteria must be fulfilled, however. The most important of these are that pulmonary vascular resistance is low without distortion of the pulmonary arteries,[8] and that the single ventricle has well preserved function. If ventricular function is poor or there is atrioventricular valve regurgitation, ventricular end diastolic pressure and left atrial pressure will be raised. The systemic venous pressure necessary to sustain a Fontan circulation will then be raised so high that oedema, ascites, and pleural effusions will accumulate. It is not surprising, therefore, that ventricular hypertrophy (which will increase ventricular 'stiffness') is an adverse risk factor for the success of a Fontan operation, even when the above criteria are fulfilled.[9] The systemic venous pressure measured early in the postoperative period is a reliable

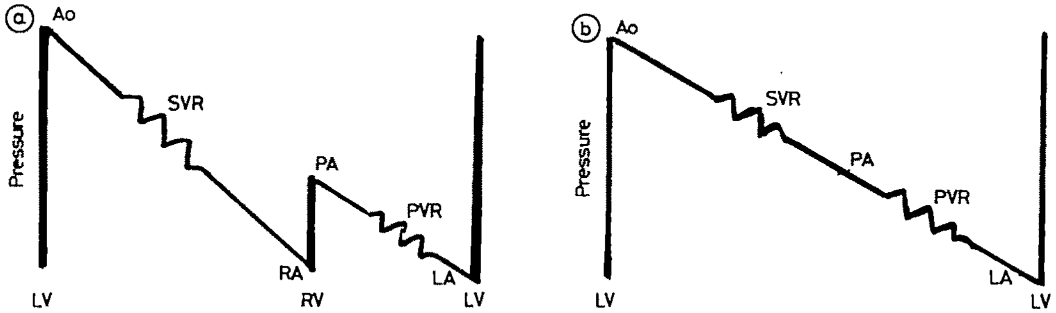


Fig 3 *Schematic representation of the resistances encountered in (a) the normal circulation, (b) the Fontan circulation, with bypass of the right heart. (Reproduced by permission of MTP Press Ltd, Lancaster.[7]) Ao=aorta; PA=pulmonary artery; PVR=pulmonary vascular resistance; SVR=systemic vascular resistance; RA=right atrium; LA=left atrium; LV=left ventricle; RV=right ventricle.*

predictor of a good result after a Fontan operation. There is a rapid increase in the probability of early death if the mean pressure exceeds 15 mm Hg.[9]

The original Fontan operation was described for the treatment of classical tricuspid atresia and incorporated a valved conduit between the right atrium and pulmonary artery.[6] Since then numerous modifications of the procedure have been undertaken and the concept extended to the wider range of cardiac malformations described above. Direct right atrial to pulmonary artery connections became fashionable when it was shown that a valve between right atrium and pulmonary artery was unnecessary.[7] The most recent development has been to connect the systemic veins rather than the right atrium to the pulmonary artery, creating total cavopulmonary rather than atriopulmonary connection.[10] This requires a channel within the right atrium directing inferior vena caval and hepatic venous blood to the pulmonary artery, while a direct anastomosis is made between the superior vena cava and the pulmonary artery (fig 4). There are a number of potential advantages. Flow disturbance to systemic venous return in the large capacity right atrium is avoided. The right atrium is not distended and hypertensive, which is inevitably the case with atriopulmonary connection, thereby possibly reducing the risk of late supraventricular arrhythmias. The coronary sinus continues to drain into the low pressure atrium and thence into the ventricle, together with pulmonary venous blood. Maintenance of this low pressure outlet for coronary sinus blood flow may have important beneficial effects on long term ventricular function.[11] Total cavopulmonary connection is of particular advantage in mitral atresia, or when a common atrioventricular valve forms the double inlet univentricular connection, or in defects with bilateral superior venae cavae.

Management considerations

Current management should be directed at giving the infant whose heart has one ventricle the best chance of a successful Fontan procedure. Palliative surgery in the neonatal period or early infancy is no longer required merely for survival or symptoms, but should be considered as preparation for an anticipated Fontan procedure. Care must be taken not to distort pulmonary artery anatomy if a palliative systemic to pulmonary artery shunt is required. On the other hand, when there is high pulmonary blood flow at high pressure the lungs should be protected from development of even mild pulmonary arteriolar thickening because maintenance of low pulmonary vascular resistance is crucial.[8] The conventional palliative operation car-

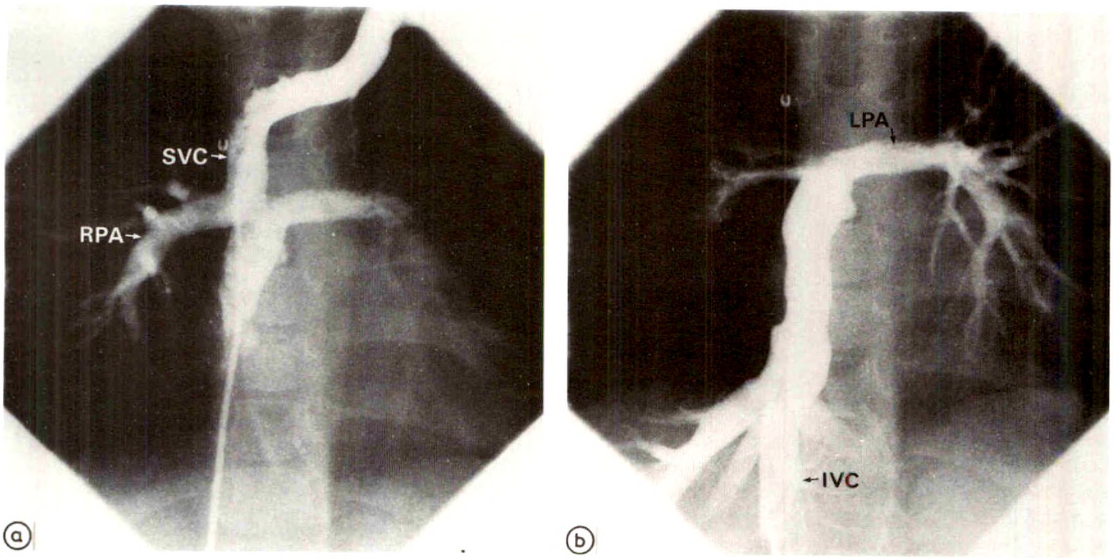


Fig 4 *Anteroposterior angiocardiograms showing a total cavopulmonary connection: (a) injection of contrast into superior vena cava, which has been anastomosed to the right pulmonary artery; (b) injection of contrast into the inferior vena cava, showing drainage of inferior vena caval and hepatic venous blood through a channel in the right atrium, which is connected to the pulmonary artery with the stump of the previously transected superior vena cava. IVC=inferior vena cava; LPA=left pulmonary artery; RPA=right pulmonary artery; SVC=superior vena cava.*

ried out under these circumstances has been pulmonary artery banding, but initial palliation by pulmonary artery banding has been associated with an unacceptably high incidence of development of subaortic stenosis in the presence of a rudimentary subaortic ventricle (fig 2)[12] although the problem may be largely confined to those infants who also have coarctation of the aorta (Franklin RCG, Deanfield JE, Anderson RH, *et al*, unpublished observations).[4] The combination of obstruction to pulmonary outflow from the pulmonary artery band together with developing systemic outflow obstruction is a potent stimulus to hypertrophy of the dominant ventricle, and mitigates against the success of an eventual Fontan procedure. Consequently, it seems that more aggressive surgery in early infancy may be necessary if the long term outlook of this group is to be improved. A direct pulmonary artery to ascending aortic connection can bypass the existing or potential area of subaortic obstruction, with pulmonary blood flow secured by means of a systemic to pulmonary shunt.[13-15] The nature of this palliative approach is similar to the one used in the management of the hypoplastic left heart syndrome.[16] The aim of all these palliative procedures is to prepare the circulation for a definitive Fontan type of operation at a later date.

The concern about ventricular hypertrophy as an adverse risk factor has led to recommendations that the definitive procedure should be performed at 2 or 3 years of age in suitable candidates.[8,9] This presents a dilemma to clinicians, most of whom would prefer to defer high risk surgery for children who only have minimal symptoms. The risk inherent in waiting for symptomatic deterioration, however, is the inevitable progression of ventricular hypertrophy in a volume loaded ventricle. This will increase the risk of the definitive operation and prejudice the functional result.

Conclusions

How well are children who have had a 'good' result from a Fontan operation? Although many are apparently asymptomatic, objective assessment has shown that resting cardiac output (Knight WB, Busst CM, Rigby ML, Shinebourne EA, Lincoln C. Haemodynamics following modified Fontan operation. Presented at Ninth Asian Pacific Congress of Cardiology, 1987) and maximal cardiac output on exercise[17] remain below normal. In addition, long term follow up information is lacking about the effect of persistently raised systemic venous pressure and its diminished flow velocity, the possible deterioration in ventricular function with time and the development of arrhythmias. Children with Fontan circulations are also inevitably at increased risk when intercurrent respiratory infections cause increases in pulmonary vascular resistance that would be unimportant to a normal heart.

Definitive surgery is now available, however, to many children with complex congenital heart disease who were previously considered inoperable. Despite these reservations, the results in the first decade after the introduction of this unique surgical approach have been encouraging. Concurrent rapid advances have occurred in the fields of heart and heart/lung transplantation. These offer an alternative form of definitive surgery for children who are unsuitable for, or who have had a poor result from, a Fontan type of operation.

References

[1] Anderson RH, Ho SY. The diagnosis and naming of congenitally malformed hearts. In: Macartney FJ, ed. *Congenital heart disease*. Lancaster: MTP Press, 1986:1–34.

[2] Anderson RH, Macartney FJ, Tynan M, *et al*. Univentricular atrioventricular connexion—the single ventricle trap unsprung. *Pediatr Cardiol* 1983;**4**:273–80.

[3] Scott DJ, Rigby ML, Miller GAH, Shinebourne EA. The presentation of symptomatic heart disease in infancy based on 10 years' experience (1973–82). *Br Heart J* 1984;**52**:248–57.

[4] Franklin RCG, Sullivan ID, Thoele DE, Macartney FJ, Anderson RH, Deanfield JE. Fate of children with tricuspid atresia presenting in infancy. *Br Heart J* 1988;**59**:122.

[5] Anderson RH, Macartney FJ, Shinebourne EA, Tynan M, eds. Tricuspid atresia. In: *Paediatric cardiology*. Vol 2. London: Churchill Livingstone, 1987:675–96.

[6] Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax* 1971;**26**:240–8.

[7] Bull C. Atrial and ventricular dependent circulations. In: Macartney FJ, ed. *Congenital heart disease*. Lancaster: MTP Press, 1986:35–53.

[8] Mayer JE, Helgason H, Jonas RA, *et al*. Extending the limits for modified Fontan procedures. *J Thorac Cardiovasc Surg* 1986;**92**:1021–8.

[9] Kirklin JK, Blackstone EH, Kirklin JW, Pacifico AD, Bargeron LM, Jr. The Fontan operation. Ventricular hypertrophy, age, and date of operation as risk factors. *J Thorac Cardiovasc Surg* 1986;**92**:1049–64.

[10] de Leval M, Bull C, Kilner P. Total cavopulmonary connection, a logical alternative to atriopulmonary connection for complex Fontan operations. Experimental studies and early clinical experience. *J Thorac Cardiovasc Surg* 1988 (in press).

[11] Ilbawi MN, Idriss FS, Muster AJ, *et al*. Effects of elevated coronary sinus pressure on left ventricular function after the Fontan operation. *J Thorac Cardiovasc Surg* 1986;**92**:231–7.

[12] Freedom RM, Benson LN, Smallhorn JF, Williams WG, Trusler GA, Rowe RD. Subaortic stenosis, the univentricular heart, and banding of the pulmonary artery: an analysis of the courses of 43 patients with univentricular heart palliated by pulmonary artery banding. *Circulation* 1986;**73**:758–64.

[13] Lin AE, Laks H, Barber G, Chin AJ, Williams RG. Subaortic obstruction in complex congenital heart disease: management by proximal pulmonary artery to ascending aorta end to side anastomosis. *J Am Coll Cardiol* 1986;**7**:617–24.

[14] Rothman A, Lang P, Lock JE, Jonas RA, Mayer JE, Castaneda AR. Surgical management of subaortic obstruction in single left ventricle and tricuspid atresia. *J Am Coll Cardiol* 1987;**10**:421–6.

[15] Freedom RM. The dinosaur and banding of the main pulmonary trunk in the heart with functionally one ventricle and transposition of the great arteries: a saga of evolution and caution. *J Am Coll Cardiol* 1987;**10**:427–9.

[16] Jonas RA, Lang P, Hansen D, Hickey P, Castaneda AR. 1st-stage palliation of hypoplastic left heart syndrome: the importance of coarctation and shunt size. *J Thorac Cardiovasc Surg* 1986;**92**:6–13.

[17] Driscoll DJ, Danielson GK, Puga FJ, Schaff HV, Heise CT, Staats BA. Exercise tolerance and cardiorespiratory response to exercise after the Fontan operation for tricuspid atresia or functional single ventricle. *J Am Coll Cardiol* 1986;**7**:1087–94.

Correspondence to Dr I Sullivan, Cardiothoracic Unit, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

Archives of Disease in Childhood, 1989, **64,** 172–175

Current topic

Is the prevalence of asthma changing?

H R ANDERSON

Department of Clinical Epidemiology and Social Medicine, St George's Hospital Medical School, London

There appears to be a widespread belief that asthma in children is increasing in the United Kingdom. This idea may have sprung from paediatricians whose clinical experience, supported by admission statistics, suggests that wheezing illness comprises an increasing proportion of their work. It will also have been fuelled by reports that mortality in young people may be increasing,[1] and that there has been an increase in patient consulting rates in general practice.[2] The spectre of the 1960s epidemic of asthma deaths lingers to remind us that mortality may be subject to unexpected change. But how well founded is the belief that prevalence is changing? In attempting to answer this question I shall briefly review trends in available indicators of asthma morbidity in children.

What is meant by prevalence?

Prevalence may refer to the proportion of the population with evidence of asthma: (a) at the point of enquiry (point prevalence); (b) over a defined prior period (period prevalence); or (c) at any time in their life (life time prevalence). Point prevalence is the easiest to measure precisely but because of the fluctuating nature of asthma will tend to underestimate the problem. Life time prevalence is often used but is seriously affected by failure (frequently selective) of recall. Period prevalence, usually over the previous year, is the compromise measure now usually adopted.

Prevalence of what?

Asthma is the label for a condition that is characterised symptomatically by wheezy dyspnoea that varies over time either spontaneously or as a result of treatment. The most widely agreed definition is based on the physiological criterion of variable limitation of airflow,[3] but this is difficult to apply in epidemiological studies and there is little agreement about how to express variability or about how much variability constitutes 'asthma'. The demonstration of hyper-responsiveness of the airways to exercise or pharmacological agents has been used in epidemiological surveys but is subject to problems of interpretation because it lacks specificity for asthma, and has, at usual cut off levels, insufficient sensitivity to identify asthma which is mild or in remission. In any case, serial data using these measures are not available to examine trends over time.

The presence of a diagnosis of 'asthma' is of little use epidemiologically. Wheezing that is mild, does not present as 'attacks', is infrequent, or which occurs only with infection may not be labelled as 'asthma'. Doctors vary in the way they label wheezing illness and in other clinical decisions such as referral and drug prescribing.[4 5] Families also vary in their willingness to accept the label. All of these factors might change over time. Thus any analysis of trends that relies on diagnosed asthma or its treatment must be interpreted with caution.

The symptom of wheeze remains the cornerstone of the epidemiological assessment of asthma on a large scale and is all that is available to examine trends. However, there is no agreed way of grading wheeze symptom by severity. Wheeze questions often refer to 'attacks' but a proportion of wheezy children do not have attacks.[6] The use and interpretation of the term 'wheeze' might also be subject to trends over time.

Prevalence surveys

Planned serial prevalence surveys of wheezing illness have not been carried out in the United Kingdom. One must therefore rely on a motley collection of studies that have varied in the questions asked, methods by which the information was elicited, age of the children, size and type of sample, and locality. These are summarised in the table.[6-20] Estimates of prevalence of wheezing over the last year or which was described as 'current' or 'recent' show little evidence of a trend; the most recent estimate of 11·5% from Nottingham in 1986 is the

Table *Prevalence studies of childhood asthma and wheezing in the United Kingdom*

Year of study	*Reference No*	*Area*	*Age of subjects (years)*	*No of subjects*	*Prevalence (%)*				
					Wheeze			*Asthma*	
					Last year	*Recent*	*Ever*	*Recent*	*Ever*
1964	7	Aberdeen	10–15	2511		11·5		4·8	
1964	8	Isle of Wight	9–11	3300				2·3	
1965	9, 10	National	7	14571	8·1		18·3		3·1
1967	11	Kent	5–14	10971					3·8
1968–	12	North West London	5	2037			24·9		3·2
1968/9	13	Birmingham	5–18	20958		5·4	9·9	2·3	4·2
1969	14	National	11	13557	4·9		12·3	2·0	3·5
1973	15	South Wales	12	817	10·2		17·0	4·2	
1974	16	Birmingham	5–6	3773		7·5		2·3	
			15–16	3681		4·3		2·4	
1975	17	National	5	12977			20·8		2·1
1978	6	South West London	9	5100	11·1		18·2	3·3	4·0
1979	18	Newcastle	7	2700	9·3				1·2
1984	19	South West London	5–13	5287	15·0		17·0		5·0
1986	20	Nottingham	5–11	4750	11·5			5·9	

same as that obtained in the earliest survey carried out in Aberdeen in 1964, and not far from the one year period prevalence of 8·1% obtained in 1965 in a national survey. The recent rate of 15·0% from South London is relatively high but may reflect the sensitivity of the particular questionnaire used. There is more variation in the prevalence of diagnosed 'asthma' with some tendency for this to increase in recent years. There has been least variation in life time prevalence of wheeze with no evidence of a trend. On the basis of these data there appears to be little reason to be concerned that the prevalence of wheezing illness in children has increased to any significant degree. Most of the variation is more plausibly explained by methodological differences than by actual changes over time.

Mortality

If, despite the fairly stable prevalence over time, asthma morbidity were increasing, the explanation would need to lie in an increase in the frequency and severity of attacks experienced by asthmatics rather than in an increase in the proportion of the population with the disease. If so, this is not reflected in mortality statistics (figure).[21] In the 0–4 year age group rates have fallen steadily. In the 5–14 age group the current rates (1985) are lower than in the late 1950s. This is despite the fact that changes in International Classification of Diseases coding rules have resulted in diagnostic transfer towards asthma as a cause of death.[22] Thus the underlying trend is probably even more encouraging than it appears.

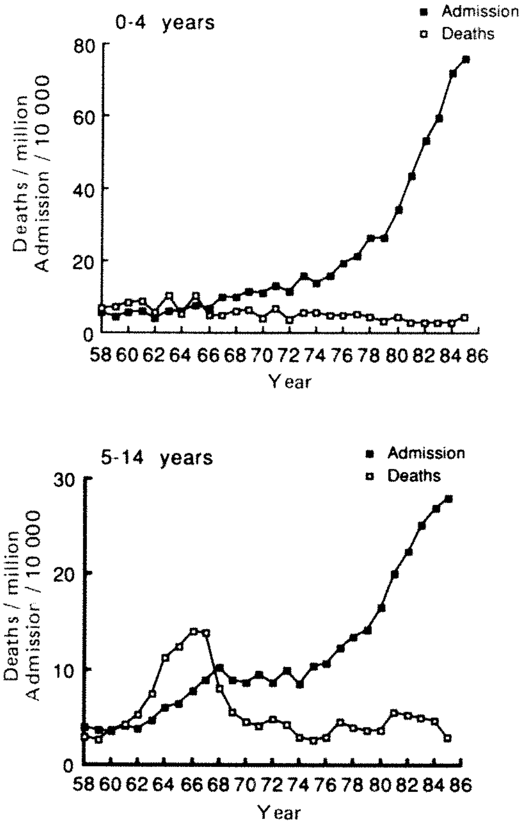


Figure *Trends in admissions and deaths for asthma in the 0–4 and 5–14 age groups. Sexes combined.*

Hospital admissions

The increase in hospital admissions for asthma has been nothing less than spectacular (figure).[23] It cannot be explained by diagnostic transfer or changes in coding.[24 25] Apart from a temporary increase in the mid 1970s, readmission rates are unchanged since 1970 indicating that more children are being admitted (HR Anderson, in preparation).[26 27] There has been a marked increase in self referral and this is related in part to the introduction of nebulisers which have increased the expectations of parents and their preference for hospital care.[27] If the increase in admissions were due to medical care factors one would predict a reduction in the severity 'threshold' for admission; however, data relating to this are meagre and equivocal. From 1960 to 1985 the average length of stay for the 5–14 age group declined from 24 to 3·7 days, and for the 0–4 age group from 11 to 2·5 days and it is likely a decline in severity has contributed to this, along with improvements in treatment.

It is important to appreciate the potential of shifts in the balance of care to increase hospital admissions. It can be estimated from surveys and routine data that in one year, among 10 000 children aged 5–14, 1100 will have episodes of wheezing and at least 150 will experience severe attacks at least once.[6] About 18 will be admitted a total of 27 times.[26] Thus a relatively small shift in the ways in which families and their general practitioners make decisions in the community could have a marked effect on hospital admissions without there being any change in underlying morbidity.

General practice

Surveys of volunteer general practices in 1970–1 and 1981–2 have found an increase in patients consulting rates for asthma for the 0–15 age group of 80% for boys and 112% for girls.[2] However, the base for this increase is fairly low (2% boys and 1% girls). Thus the increase could easily reflect an increase in presentation to the general practitioner. Equally important there is the likelihood that the diagnosis of asthma is being more frequently applied by general practitioners after reports of substantial underdiagnosis of asthma in wheezy children.[4 5] This is supported to some extent by recent survey evidence.[20]

Conclusion

Data directly related to prevalence are not entirely satisfactory but such that exist do not support the assertion that there has been an increase in the proportion of the child population who experience wheezing illness. If, nevertheless, asthma is increasing it must therefore be due to an increase in severity but there is no direct evidence concerning this. An indirect indicator, mortality, is not increasing. The increase in hospital use could be explained by a shift in the balance of care due to medical care factors, though it is interesting that readmissions have not increased. The increase in utilisation of general practitioners could be due to diagnostic transfer as well as to an increased tendency of families to seek consultation. An attitude of scepticism is appropriate. Nevertheless, because of the importance of this issue, consideration should be given to the setting up of a simple method of conducting serial surveys among samples of the child population to monitor the situation over the coming years.

References

[1] Burney PGJ. Asthma mortality in England and Wales: evidence for a further increase 1974–84. *Lancet* 1986;**ii:**323–6.

[2] Fleming DM, Crombie DL. Prevalence of asthma and hay fever in England and Wales. *Br Med J* 1987;**294:**279–83.

[3] Scadding JS. Definition and clinical categories of asthma. In: Clark TJH, Godfrey S. eds. *Asthma.* London: Chapman and Hall, 1977:1–10.

[4] Anderson HR, Bailey PA, Cooper JS, Palmer JC. Influence of morbidity, illness label, and social, family and health service factors on drug treatment of childhood asthma. *Lancet* 1981;**ii:** 1030–2.

[5] Speight ANP, Lee DA, Hey EN. Underdiagnosis and undertreatment of asthma in childhood. *Br Med J* 1983;**286:**1255–8.

[6] Anderson HR, Bailey PA, Cooper JS, Palmer JC, West S. Morbidity and school absence caused by asthma and wheezing illness. *Arch Dis Child* 1983;**58:**777–84.

[7] Dawson B, Horobin G, Illsley R, Mitchell R. A survey of childhood asthma in Aberdeen. *Lancet* 1969;**i:**827–30.

[8] Graham PJ, Rutter ML, Yule W, Pless IB. Childhood asthma. A psychosomatic disorder? Some epidemiological considerations. *British Journal of Preventive and Social Medicine* 1967;**21:** 78–85.

[9] Davie R, Butler NR, Goldstein H. *From birth to seven.* London: Longman, 1972.

[10] Anderson HR, Bland JM, Patel S, Peckham C. The natural history of asthma in childhood. *J Epidemiol Community Health* 1986;**40:**121–9.

[11] Hamman RF, Halil T, Holland WW. Asthma in schoolchildren: Demographic associations and peak expiratory flow rates compared with children with bronchitis. *British Journal of Preventive and Social Medicine* 1975;**29:**228–38.

[12] Leeder SR, Corkhill R, Irwig LM, Holland WW, Colley JRT. Influence of family factors on the incidence of lower respiratory illness during the first year of life. *British Journal of Preventive and Social Medicine* 1976;**30:**203–12.

[13] Morrison Smith J, Harding LK, Cumming G. The changing prevalence of asthma in school children. *Clin Allergy* 1971;**1:** 57–61.

[14] Peckham C, Butler N. A national study of asthma in childhood. *J Epidemiol Community Health* 1978;**32:**79–85.

[15] Burr ML, Eldridge BA, Borysiewicz LK. Peak expiratory flow rates before and after exercise in schoolchildren. *Arch Dis Child* 1974;**49:**923–6.

[16] Morrison Smith J. The prevalence of asthma and wheezing in children. *Br J Dis Chest* 1976;**70:**73–7.

[17] Golding J, Butler NR. Wheezing and asthma. In: Butler NR.

Golding J, eds. *From birth to five: a study of the health and behaviour of Britains 5-year-olds*. Oxford: Pergamon Press, 1986:158–70.

[18] Lee DA, Winslow NR, Speight ANP, Hey EN. Prevalence and spectrum of asthma in childhood. *Br Med J* 1983;**286**:1256–8.

[19] Johnston IDA, Bland JM, Anderson HR. Ethnic variation in respiratory morbidity and lung function in childhood. *Thorax* 1987;**42**:542–8.

[20] Hill R, Tattersfield AE. Asthma in children: a comparison of community surveys in the UK. *Thorax* 1988;**43**:258–9.

[21] Office of Populations Censuses and Surveys, Welsh Office. *Mortality statistics*. London: HMSO, Published annually. (Series DHI).

[22] Stewart CJ, Nunn AJ. Are asthma mortality rates changing? *Br J Dis Chest* 1985;**79**:229–34.

[23] Department of Health and Social Security and Office of Population Censuses and Surveys, Welsh office. *Hospital Inpatient Enquiry*. London: HMSO, Published annually.

[24] Anderson HR. Increase in hospitalisation for childhood asthma. *Arch Dis Child* 1978;**53**:295–300.

[25] Khot A, Burn R, Evans N, Lenney C, Lenney W. Seasonal variation and time trends in childhood asthma in England and Wales 1975–81. *Br Med J* 1984;**289**:235–7.

[26] Anderson HR, Bailey P, West S. Trends in the hospital care of acute childhood asthma 1970–8: a regional study. *Br Med J* 1980;**281**:1191–4.

[27] Storr J, Barrell E, Lenney W. Rising asthma admissions and self referral. *Arch Dis Child* 1988;**63**:774–9.

Correspondence to Professor HR Anderson, Department of Clinical Epidemiology and Social Medicine, St George's Hospital Medical School, Cranmer Terrace, Tooting, London SW17 0RE.

Archives of Disease in Childhood, 1989, **64,** 176–180

Correspondence

Clinical outcome of fetal uropathy

Sir,

Madarikan *et al*, in their article on clinical outcome of fetal uropathy, discussed the antenatal management of fetal uropathy.[1] However, I think the following points deserve mention.

Any fetus found to have a renal dysplasia or an obstructive uropathy should, initially, have a full anomaly ultrasound scan performed to exclude other structural abnormalities. An accurate ultrasound scan can normally be done even in the presence of oligohydramnios by an experienced ultrasonographer. A fetal karyotype should also be considered because of the association between renal tract abnormalities and chromosomal defects.[2] The parents should then be counselled with this information and its significance. If they elect to continue the pregnancy an attempt is made to assess the functional potential of the fetal renal tract by three methods: amniotic fluid volume, kidney size and sonographic appearances, and by the results of biochemical analysis of fetal urine after ultrasound guided needle aspiration. This latter technique is particularly helpful in identifying those fetuses with an obstructive uropathy who could benefit from vesicoamniotic shunting. Appleman and Golbus have shown that a fetal urine osmolality greater than 210 mmol/kg and a urinary sodium and potassium greater than 100 mmol/l and 90 mmol/l respectively, are accurate predictors of renal function.[3] If the kidneys are non-dysplastic, liquor volume is reduced and the obstructive uropathy is infravesical, then vesicoamniotic shunting is generally undertaken. This has been shown to improve the perinatal survival of fetuses with posterior urethral valves, prune-belly syndrome, and urethral atresia. Whether it reduces long term renal and pulmonary morbidity is, however, unknown.

Although no one doubts the value of ultrasound screening, controversies do remain regarding the antenatal management of obstructive uropathy. Further information comparing conservative and surgical treatment of fetal obstructive uropathy is required, not only in relation to perinatal survival, but also long term morbidity and mortality.

References

[1] Madarikan BA, Hayward C, Roberts GM, Lari J. Clinical outcome of fetal uropathy. *Arch Dis Child* 1988;**63:**961–3.

[2] Manning F. International fetal surgery registry: 1985. Update. *Clin Obstet Gynecol* 1986;**29:**551–7.

[3] Appleman Z, Golbus M. The management of fetal urinary tract obstruction. *Clin Obstet Gynecol* 1986;**29:**482–9.

J Campbell
Department of Obstetrics and Gynaecology,
St Bartholomew's Hospital,
London EC1A 7BE

Brittle or battered?

Sir,

Most paediatricians know very little about osteogenesis imperfecta. From time to time they are called upon to give 'expert' evidence in a case where a child has unexplained fractures. In most cases the differential diagnosis is obvious, but in others not quite so straightforward as Dr H Carty would have us believe.[1]

My concern is that paediatricians faced with the task of providing expert evidence will refer to Dr Carty's authoratative annotation and in consequence may mislead the court. It is in the mild case of osteogenesis imperfecta in which the sclerae are normal colour and the teeth normal that most diagnostic difficulty arises. Paediatricians faced with the onerous task of providing an explanation for fractures should bear in mind the following points[2]:

- No family history is necessary for the diagnosis of brittle bones.
- Wormian bones are **not** a *sine qua non* for the diagnosis of osteogenesis imperfecta.
- Metaphyseal fractures are a feature of both abuse and brittle bones.
- Normal bone texture and a normal radiographic appearance of the rest of the skeleton at the time of the first fracture do not exclude brittle bones.
- The fact that no recurrent fractures occur while the child is in care does **not** exclude the diagnosis of osteogenesis imperfecta. The interval between fractures may be many months or even years.

I believe that in very rare instances at the time of court proceedings it may not be possible to differentiate accurately brittle bones from non-accidental injury on the medical evidence alone.

References

[1] Carty H. Brittle or battered. *Arch Dis Child* 1988;**63:**350–2.

[2] Paterson CR, McAllion SJ, Shaw JW. Clinical and radiological features of osteogenesis imperfecta type IVA. *Acta Paediatr Scand* 1987;**76:**548–52.

I Blumenthal
Oldham and District General Hospital,
Rochdale Road,
Oldham OL1 2JH

Dr Carty comments:

The diagnosis of mild osteogenesis imperfecta can be difficult but poses a clinical problem only in older children who are mobile and sustain frequent fractures after minor injury. Medico-legal problems arise, not with these children, but with children, usually under the age of 6 months, who have suffered non-accidental injury and who, it is claimed, have mild osteogenesis imperfecta despite the absence of a family history and the presence of stigmata classically characteristic of non-accidental injury: complex skull fractures, metaphyseal fractures, rib fractures, and fractures at different stages of healing. Fractures sustained by children with mild osteogenesis imperfecta are the same as accidental fractures sustained by normal children: typically fractures of the shafts of long bones. Astley states that metaphyseal fractures are found only in severe osteogenesis imperfecta and not in mild cases.[1] Rib and skull fractures occur in mild osteogenesis imperfecta with the same frequency as they do in normal children. The only series describing metaphyseal, skull, and rib fractures as a prominent feature of mild osteogenesis imperfecta is the series of Paterson quoted by Dr Blumenthal. I am sure that Dr Blumenthal has read the ensuing correspondence from Taitz[2] who points out that not all courts have accepted Paterson's evidence. Taitz has calculated, with support of several authoritative references,[3] that the chance of a child having a mild form of osteogenesis imperfecta without a family history is between 1:1 000 000 and 1:3 000 000.

The third statement (about metaphyseal fractures) in Dr Blumenthal's letter is quoted directly from Paterson who in turn claims authority from Astley[1] but Astley's full quotation is: 'There is evidence of obvious generalised bone disease of osteogenesis imperfecta so that confusion with non-accidental injury does not occur'.

For these reasons I cannot accept Dr Blumenthal's claim that courts will be misled by what I have written.

References

[1] Astley, R. Metaphyseal fractures in osteogenesis imperfecta. *Br J Radiol* 1979;**52**:441–3.

[2] Taitz LS. Child abuse and osteogenesis imperfecta. *Br Med J* 1988;**296**:292.

[3] Taitz LS. Child abuse and osteogenesis imperfecta. *Br Med J* 1987;**295**:1082–3.

Non-accidental injury and copper deficiency

Sir,

Recent excellent articles by Dr Helen Carty[1] and Dr J C L Shaw[2] on non-accidental injury and copper deficiency correctly and clearly state that the court is not the right place to decide on the child's welfare. I tend to agree with them. It appears that on both prosecution and defence sides winning a case if often of more importance than the truth. In achieving this each side tries to exploit the subtle nature of the medical evidence presented by the so called expert witnesses; this evidence has to be grasped and decided upon by the non-medical judges and juries—an almost impossible task. In my opinion the medical experts are as much to blame as the non-medical law profession in compromising the child's welfare. Surely society and the medical profession, as part of society, should not accept this unsatisfactory situation and should campaign for a system, perhaps away from the courts, which seeks the real truth and ultimately does justice to the child.

References

[1] Carty H. Brittle or battered. *Arch Dis Child* 1988;**63**:350–2.

[2] Shaw JCL. Copper deficiency and non-accidental injury. *Arch Dis Child* 1988;**63**:448–55.

K J SHAH
The Children's Hospital,
Birmingham B16 8ET

Good tolerance of pyrazinamide in children with pulmonary tuberculosis

Sir,

By adding pyrazinamide to the usual triple treatment consisting of rifampicin, isoniazid, and ethambutol, it is possible to reduce the duration of antituberculous treatment with equal efficacy.[1] Despite recommendations[2] paediatricians seem reluctant to prescribe pyrazinamide, probably because of fear of hepatotoxicity and effects on uric acid metabolism.

We have assessed the tolerance of pyrazinamide in 43 children with primary tuberculosis and abnormalities on chest radiography (principally hilar lymphadenopathy with or without parenchymal infiltration). The diagnosis of tuberculosis was confirmed by a positive Mantoux test ($>$10 mm) and the finding of *Mycobacterium tuberculosis* in the children or their parents, or both. Mean age at diagnosis was 6 years (range 2 months to 15 years). Nineteen children were less than 3 years old.

Each morning, one hour before breakfast, during the initial phase all the children received rifampicin, isoniazid, and ethambutol at recommended paediatric doses[3] and pyrazinamide (mean dose 23·3 mg/kg, range 20 to 37 mg/kg).

This regimen of four drugs was prescribed for two months in 38 children, three months in two, and four months in three children (because of initial resistance to isoniazid). The second phase of treatment consisted of daily rifampicin and isoniazid.

Plasma uric acid and plasma glutamic oxaloacetic and glutamic pyruvate transaminases were measured before initiation of treatment, one month later, and at the end of treatment with pyrazinamide. Plasma uric acid concentrations were normal before treatment (150–360 μmol/l). They increased slightly (360–450 μmol/l) in nine of the children (21%) and returned to normal when pyrazinamide was stopped. There were no signs of gout nor arthralgias.

Liver enzymes were normal before treatment in 42 children and remained normal in 40. In two children transaminases increased (to three times normal values) at one month but returned to normal without modification of treatment. In one child the four antituberculous drugs were started just after viral A hepatitis; this did not prevent the normalisation of liver functions.

This paediatric study is in agreement with those carried out in adults and shows that pyrazinamide is well tolerated when used in doses $<$35 mg/kg/day even in infants. Furthermore, except in those five children with initial resistance to isoniazid, the duration of treatment was reduced to six months, which compares favourably with the classical nine month regimen containing rifampicin, isoniazid, and ethambutol.

References

[1] Hong Kong Chest Service/British Medical Research Council. Five year follow-up of a controlled trial of five 6-month regimens of chemotherapy for pulmonary tuberculosis. *Am Rev Respir Dis* 1987;**136:**1339–42.

[2] American Thoracic Society. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am Rev Respir Dis* 1986;**134:**355–63.

[3] Smith MHD, Marquis JR. Tuberculosis and other mycobacterial infections: management of tuberculous children. In: Feigin RD, Cherry JD, eds. *Textbook of pediatric infectious diseases*. Philadelphia: WB Saunders, 1987:1370–3.

M LE BOURGEOIS, J DE BLIC, J PAUPE, and P SCHEINMANN
Service d'Allergologie et de Pneumologie Infantiles,
Hopital des Enfants Malades, 149 rue de Sèvres,
75730 Paris Cedex 15, France

Accidental poisoning

Sir,

Dr Craft's annotation on accidental poisoning raises some interesting points.[1] The Republic of Ireland has no regulations concerning use of child resistant containers or closures. Despite considerable effort and input into public education (return used medicines campaigns, 'play it safe' series, posters, and television campaigns by the Health Education Bureau and others, etc) the number of children attending our hospital after accidental drug ingestion has not altered (table).

Table *No of children attending hospital after accidental drug ingestion*

Ingestions	*1975*[2]	*1980*[3]	*1983*[4]	*1987*
Total No of children	322	237	323	2[illegible]0
Salicylates	67	34	30	[illegible]1
Paracetamol	19	24	40	40

In 1987 a working party convened by the Faculty of Paediatrics of the Royal College of Physicians of Ireland concluded that application of child resistant containers to *all* medications on a regulatory or voluntary basis could be counter productive, especially where the drug contained therein was not toxic (vitamins, antibiotics, etc). It tried to select out those drugs which are most commonly ingested or most potentially toxic and recommended that they be dispensed in child resistant containers. The following groups of drugs were included:

- Aspirin, paracetamol, and other analgesics
- Non-steroidal anti-inflammatory agents
- Iron (haematinics)
- Antihistamines, including antitussives and decongestants
- Anticonvulsants
- Digoxin
- Theophylline and derivatives
- Sedatives, hypnotics, and tranquillisers
- Tricyclic and other antidepressants
- Opiate derivatives, including preparations containing diphenoxylate
- Appetite suppressants

It was estimated that the above groups of drugs account for about 60–70% of accidental ingestions presenting to hospital. It was suggested that ordinary containers could be provided on the request of patients, to old or disabled people, or at the discretion of the prescribing doctor or dispensing pharmacist.

The secret of success in accident prevention is access prevention. Child resistant containers constitute the most consistent method of prevention. Every consequence of accidental poisoning (induced emesis, gastric lavage, hospital admission, intravenous fluids) is extremely unpleasant to that most vulnerable group—toddlers and preschool children.

It never ceases to amaze me how little apparent consumer resistance there is to some everyday individually wrapped items (milk, marmalade, mayonnaise, peanuts) which can be extremely difficult to open. Therefore on with child resistant containers in a wider range of medications and household chemicals!

Finally, there is one commercial closure for use with liquids—'Squeez 'N Turn' (United Closures and Plastics).

References

[1] Craft AW. Accidental poisoning. *Arch Dis Child* 1988;**63:**584–6.

[2] Gill DG, Dargan D, McDaid T. Accidental poisoning of children—a years experience in an accident and emergency department. *Ir Med J* 1976;**69:**375–8.

[3] Gill DG. Accidental poisoning of children. 1975 versus 1980. *Ir Med J* 1982;**75:**160–1.

[4] Gill DG, Lavelle J. Accidental poisoning of children. *Irish Pharmaceutical Journal* 1984;**62:**141–4.

D G GILL
Department of Paediatrics,
Children's Hospital,
Temple St,
Dublin 2

Isolated pulmonary histiocytosis

Sir,

Isolated pulmonary histiocytosis is indeed a rare disorder, but it is not as rare as reported by McDowell *et al* in their article.[1] In world literature, 11 cases of isolated pulmonary histiocytosis in the paediatric age group have been reported.[2]

The prognosis of isolated pulmonary histiocytosis is grave. Of 11 reported cases, six died within one year of diagnosis.[2] Most of these patients were treated with a combination of steroids and alkylating agents. Nondahl *et al* reported one case who improved with steroids alone.[2]

We recently treated a girl aged 1½ years with steroids; however, she did not show any clinical response. She eventually improved with 6-mercaptopurine in a dose of 75 mg/m^2. We suggest that these patients should be given an initial trial of steroid for four to six weeks. If the response is poor or inadequate, treatment with alkylating agents or antimetabolites is warranted.

References

[1] McDowell HP, Macfarlane PI, Martin J. Isolated pulmonary histiocytosis. *Arch Dis Child* 1988;**63**:423–6.

[2] Nondahl SR, Finlay JL, Farrell PM, Warner TF, Hong R. A case report and literature review of 'primary' pulmonary histiocytosis of childhood. *Med Pediatr Oncol* 1986;**14**:57–62.

N K Arora *and* R Koyyana
Department of Paediatrics,
All India Institute of Medical Sciences,
Ansari Nagar, New Delhi 110 029,
India

Cerebral arterial air embolism in experimental neonatal pneumothorax

Sir,

Fenton *et al* reported five cases of air embolism in ventilated very low birthweight infants with fatal outcome.[1] Two of the infants had pneumothorax, in one case on both sides. They have said, that 'air embolism represents the extreme end of the range of air leaks' in the perinatal period.

We have observed the pial-arachnoideal microcirculation intravitaly (Wild Photomacroscope) on anaesthetised, immobilised, and artificially ventilated newborn piglets during the course of induced bilateral pneumothorax.[2 3] Up to now we have studied 30 animals and in three cases we have found artificial cerebral arterial air microembolisation with fatal outcome within minutes. The affected microvessels showed significant vasoconstriction with the rapid cessation of the blood flow (figure). Concomitantly, air bubbles were seen in the umbilical arterial blood sample in all three cases.

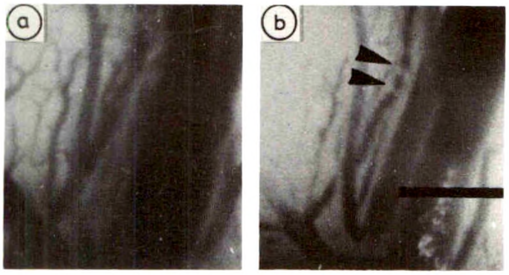


Figure *Intravital microphotographs of the parietal pial-arachnoideal microvessels in a newborn piglet (a) before and (b) 40 minutes after the induction of experimental pneumothorax. Arrows point to the arterial air emboli accompanied by severe vasoconstriction. Bar=1·0 μm.*

Our in vivo observations suggest that air embolisation may occur more frequently than has been reported during neonatal air leaks and may also affect cerebral microcirculation.

Supported by the Alexander von Humboldt Foundation, Bonn, Federal Republic of Germany.

References

[1] Fenton TR, Bennett S, McIntosh N. Air embolism in ventilated very low birthweight infants. *Arch Dis Child* 1988;**63**:541–3.

[2] Temesvari P, Hencz P, Joó F, Eck E, Szerdahelyi P, Boda D. Modulation of the blood-brain barrier permeability in neonatal cytotoxic brain edema: laboratory and morphological findings obtained on newborn piglets with experimental pneumothorax. *Biol Neonate* 1984;**46**:198–208.

[3] Temesvari P, Kovacs J. Selective opening of the blood-brain barrier in newborn piglets with experimental pneumothorax. *Neurosci Lett* (in press).

P Temesvari, J Kovacs, *and* K Racz
Department of Pediatrics,
Albert Szent-Györgyi University Medical School,
Szeged, Hungary

Recurrent cot death and suffocation

Sir,

The careful study by Beal and Blundell shows an incidence of sudden infant death syndrome (SIDS) 10 times greater in the previous siblings of an infant who has died of the syndrome compared with controls.[1] They show that the circumstances and the families, in which two or more siblings died from SIDS, differed from those in which only one infant died in several important ways, including a more variable and older age at death. In postulating that 'both genetic and environmental factors seem to contribute to recurrence of SIDS in families' it is a pity that the authors do not confront the issue more squarely and acknowledge that some of these deaths will have been caused directly by the mothers—that is, filicide or homicide. In order to understand the epidemiology of SIDS better, and also to prevent deaths, it is important to recognise that a small proportion of children labelled as 'SIDS' are killed by their parents, usually their mother. Emery has suggested that between 2% and 10% of cot deaths result from filicide,[2] and in his detailed study of 12 families in Sheffield who incurred two or more cot deaths, he concluded that in five of those families filicide was either certain or probable.[3]

From my current study of 21 families in which the mother has suffocated a young child it has become apparent how often that child has originally been labelled as SIDS and contributed to false national statistics concerning the syndrome. Within these families a recurrence of unexplained, or definitely homicidal, deaths in other siblings is high; it is noteworthy that for those children previously labelled SIDS their age at death is both more variable and higher than is usual for sudden infant death syndrome.

References

[1] Beal SM, Blundell HK. Recurrence incidence of sudden infant death syndrome. *Arch Dis Child* 1988;**63**:924–30.
[2] Emery JL. Infanticide, filicide and cot death. *Arch Dis Child* 1985;**60**:505–7.
[3] Emery JL. Families in which two or more cot deaths have occurred. *Lancet* 1986;**i**:313–5.

R Meadow
Department of Paediatrics and Child Health,
St James's University Hospital, Leeds LS9 7TF

Measuring severity of injuries to children from home accidents

Sir,

We support the view expressed by Alwash and McCarthy that a severity scale of childhood accidental injury is a necessary requirement for appropriate epidemiological research.[1] We consider that for such a scale to be fully reliable, however, it should not be dependent upon treatment but rather be based on an objective assessment of the injury itself or the clinical status of the patient, or both.

Treatment dependent scales are an example of indirect severity indices and are susceptible to many biases. For example the decision to admit an injured victim to hospital will vary by place, over time, and by person (for example, social class of the patient, seniority of the attending doctor).

The use of these scales therefore introduces great difficulties into attempts to study some of the important issues relating to accidental injury in childhood—for example, outcome of different treatments, the relationship of social class to injury severity, evaluation of preventative programmes, and measures of the 'true' frequency of accidental injury in the community.

The development of objective, direct severity indices (for example, the abbreviated injury scale as alluded to by the authors) may provide one method to overcome the difficulties highlighted. This type of scaling has been applied to a paediatric population and judged to be both reliable and valid.[2 3]

Indeed in the Swedish studies of the early 1970s, Gustafsson, using the abbreviated injury scale, reported that although the actual accident frequency as recorded in hospitals had not diminished since the 1950s, there had been a shift towards less complicated injuries.[3] We therefore believe that 'direct' injury severity scaling has great importance in the evaluation of intervention programmes not only because an unbiased rate of injury in the community cannot otherwise be determined but also because as noted by Alwash and McCarthy 'plans for prevention might seek to reduce the severity of injuries, rather than their frequency'.

References

[1] Alwash R, McCarthy M. Measuring severity of injuries to children from home accidents. *Arch Dis Child* 1988;**63**:635–8.
[2] Wesson DE, Spence LJ, Williams JI, *et al*. Injury scoring systems in children. *Can J Surg* 1987;**6**:398–400.
[3] Gustafsson LH. Childhood accidents. Three epidemiological studies on the etiology. *Scand J Soc Med* 1977;**5**:5–13.

S S Walsh *and* S N Jarvis
Department of Child Health,
University of Newcastle upon Tyne,
Newcastle upon Tyne NE2 4HH

Archives of Disease in Childhood, 1989, **64,** 181–182

British Paediatric Association

Children in specialist hospital departments

The British Paediatric Association (BPA) has cooperated with several other professional associations in preparing joint statements concerning the care of children.

(1) Children's attendances at accident and emergency departments

This joint statement, issued in 1988 by the BPA, the British Association of Paediatric Surgeons, and the Casualty Surgeons Association, notes that over two million children are seen annually in accident and emergency departments, a larger number than is seen in paediatric outpatient clinics. At least 15% of these children have medical conditions and at the Children's Hospital, Sheffield, 40% of those attending the accident and emergency department under the age of 2 do so for medical conditions. In only 13 out of 189 hospitals supplying information for a survey in 1985, however, was there any regular sessional commitment to the accident and emergency department by a member of the medical paediatric staff. The joint statement goes on to make a number of important recommendations.

MEDICAL TRAINING

Paediatric accident and emergency medicine should develop as a specialty. Consultant posts in this specialty should be established in children's hospitals and possibly in large accident and emergency departments in general hospitals where many children are seen. The Joint Committee on Higher Medical Training should therefore consider drawing up an appropriate training programme to include a minimum of one year's experience at senior registrar level in paediatrics and/or paediatric surgery and a minimum of one year in an accident and emergency department where considerable numbers of children are seen. It is also recommended that a minimum of three months' experience in paediatrics should be obligatory for accreditation in accident and emergency medicine.

FACILITIES

Children's departments and accident and emergency departments should be on the same site and a consultant paediatrician should have responsibility for liaison with the consultant in accident and emergency medicine concerning the care of children.

Special accommodation is needed in accident and emergency departments for interviewing children and their families, especially in relation to child abuse. Separate waiting areas and treatment rooms for children should be provided.

NURSING

A registered sick children's nurse with managerial responsibility for the children's department should liaise with the nursing officer in the accident and emergency department concerning the arrangements for children in that department. Accident and emergency departments should have at least one registered sick children's nurse on their staff.

(2) Hospital facilities for children undergoing ear, nose, and throat treatment

This is a 1988 version of a joint statement by the BPA and the British Association of Otolaryngologists that was first issued 10 years ago.

Children in hospital for ear, nose, and throat treatment should be under the care of the otolaryngologist and their nurses should have both paediatric and ear, nose, and throat training. Paediatricians should have a general oversight of all children in hospital.

Children admitted for ear, nose, and throat treatment are best nursed in a comprehensive children's department but where this is not possible the children should be nursed in accommodation designed and staffed for their special needs. This may be in an area for ear, nose, and throat treatment in the children's ward or in a children's area in the ear, nose, and throat ward. In either case the two wards should be close to each other and have easy access to the operating theatres.

Accommodation should be available for parents wishing to stay in hospital with their children and unrestricted visiting by parents should be encouraged.

(3) Ophthalmic services for children

A joint working party between the Faculty of

Ophthalmologists and the BPA published a report in 1984. Children under the care of ophthalmologists should ideally be admitted to a children's ward where optimal ophthalmic care can be achieved and children's trained nurses and general paediatric medical care are available. If this is not possible children should be nursed in a separate part of the ophthalmic unit that has open visiting for parents and siblings and where a play leader and teacher are available.

Good liaison between paediatricians and ophthalmologists is essential and there should be a regular paediatric commitment to ophthalmic units. In the outpatient department there should be a play area and facilities for feeding babies. Separate clinics for children are desirable.

The report emphasises the importance of screening children for visual defects for which general practitioners, clinical medical officers, and health visitors should have appropriate training. Paediatricians should understand the development of normal vision and be competent to diagnose common eye disorders in children. Ophthalmologists should have some knowledge of child development and paediatric disorders.

ADM Jackson

Archives of Disease in Childhood, 1989, **64,** 183–184

Instructions to authors

Papers for publication should be sent to the Editors, *Archives of Disease in Childhood,* BMA House, Tavistock Square, London WC1H 9JR. Submission of a paper will be held to imply that it contains original work not being offered elsewhere or published previously. Manuscripts should be prepared in accordance with the Vancouver style.[1] The Editors retain the right to shorten the article or make changes to conform with style and to improve clarity.

For guidance on ethical aspects refer to the editorial in this journal.[2] All authors must sign the copyright form.

Failure to adhere to any of these instructions may result in delay in processing the manuscript and it may be returned to the authors for correction before being submitted to a referee.

General

- Authors must submit two copies of the manuscript.
- Manuscripts must have a title page which gives the title of the paper, the name of the author(s), the place where the work was carried out, and the address of the corresponding author. The authors should include their family names and initials. The number of authors should be kept to a minimum and should include only those who have made a contribution to the research: justification should be made for more than five authors. Acknowledgments should be limited to workers whose courtesy or assistance has extended beyond their paid work, and to supporting organisations. Information about the availability of reprints should be given at the end of the references.
- The article *and* references *must* be typed in double line spacing with a 5 cm margin on the left side. The right hand margin should not be justified. Pages should be numbered in the top right hand corner.
- All measurements must be in SI units apart from blood pressure measurements, which should be in mm Hg and drugs in metric units.
- Abbreviations should be used rarely and should be preceded by the words in full before the first appearance.
- Any article may be submitted to outside peer review and for statistical assessment. This may take up to six weeks. Articles are usually published within five months of the date of the final acceptance of the manuscript.
- Twenty five reprints are supplied free; further reprints may be ordered when the proof is returned. Reprints take about two months to be dispatched; those going overseas are sent by surface mail.
- If the paper is rejected the manuscript and all illustrations will normally be shredded.

Original articles

- The title should have no more than 10 words and should not include the words 'child', 'children', or 'childhood' (already implicit in the title of the journal).
- The summary should be no longer than 150 words and should set out what was done, the main findings, and their implications. Detailed statistics such as p values should not be included.

Short reports

- Length must not exceed 900 words, including a summary of less than 50 words, one or two small tables or illustrations and up to six references.
- The title should be no longer than seven words.

Annotations

- Annotations are commissioned by the editors who welcome suggestions for topics or authors.

Letters

- Letters must be typed in double line spacing, should normally be no more than 300 words, and have no more than four references and must be signed by all authors. Letters may be published in a shortened form at the discretion of the Editor.

Tables and illustrations

Tables should be submitted separately and typed in double line spacing without ruled lines.

- Avoid histograms if possible.
- Illustrations should be used only when data cannot be expressed clearly in any other way.

When graphs are submitted the numerical data on which they are based should be supplied.

- Illustrations should be no larger than single or double column width—that is 7 cm or 14·5 cm in width and be trimmed to remove all redundant areas; the top should be marked on the back.
- Patients shown in photographs should have their identity concealed or should give their written consent to publication. Ultrasound scan pictures should be arrowed on an overlay to indicate areas of interest or should be accompanied by explanatory line drawings.
- If any tables or illustrations submitted have been published elsewhere, written consent to republication should be obtained by the author from the copyright holder (usually the publisher) and the authors.

References

- References *must* numbered in the order they appear in the text and include all information:

[1] Barson AJ, Tasker M, Lieberman BA, Hillier VF. Impact of improved perinatal care on the causes of death. *Arch Dis Child* 1984;**59**:199–206.

[2] Dowling S. *Health for a change*. London: Child Poverty Action Group, 1983.

- Abstracts, information from manuscripts not yet accepted, or personal communications may be cited only in the text and not included in the references. References are not checked by us; authors must verify references against the original documents before submitting the article.

References

[1] International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1982;**284**:1766–70.

[2] Anonymous. Research involving children—ethics, the law, and the climate of opinion. [Editorial.] *Arch Dis Child* 1978;**53**: 441–2.

Revised January 1989

9.11.90

Vol 64 No 3

March 1989

ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

Annotation

When to do a lumbar puncture in a neonate *Halliday* 313

Original articles

Penetrating eye injuries *Patel* 317

Intestinal permeability in Crohn's disease *Murphy, Eastham, Nelson, et al* 321

Campylobacter pylori gastritis: long term results of treatment with amoxycillin *Oderda, Dell'Olio, Morra, et al* 326

Coarctation of the aorta corrected during the first month of life *Ehrhardt and Walker* 330

Factors associated with developmental progress of full term neonates who required intensive care *Ludman, Lansdown, and Spitz* 333

Value of selective screening for congenital adrenal hyperplasia in Hungary *Sólyom and Hughes* 338

Changes in trimethoprim pharmacokinetics after the newborn period *Hoppu* 343

Anorexia nervosa and food avoidance emotional disorder *Higgs, Goodyer, and Birch* 346

Blood selenium concentrations and glutathione peroxidase activity *Lloyd, Robson, Smith, et al* 352

Seizures presenting as apnoea *Navelet, Wood, Robieux, et al* 357

Antineutrophil cytoplasm antibodies in Kawasaki disease *Savage, Tizard, Jayne, et al* 360

Oesophageal atresia and associated anomalies *Chittmittrapap, Spitz, Kiely, et al* 364

Maternal insecurity and failure to thrive in Asian children *Fenton, Bhat, Davies, et al* 369

Energy and nutrient intakes in cystic fibrosis *Buchdahl, Fulleylove, Marchant, et al* 373

Growth and very low birth weight *Kitchen, Ford, and Doyle* 379

Weight and age at menarche *Stark, Peckham, and Moynihan* 383

Outcome of neonatal necrotising enterocolitis: results of the BAPM/CDSC surveillance study, 1981–84 *Palmer, Biffin, and Gamsu* 388

Short reports

Immunoreactive trypsin in Shwachman's syndrome *Dossetor, Spratt, Rolles, et al* 395

Aetiology of Kawasaki disease *Bannister, Edwards, and Ibata* 397

Kawasaki disease in siblings *Hewitt, Smith, Joffe, et al* 398

Mildly anaemic toddlers respond to iron *Parks, Aukett, Murray et al* 400

Pseudocardiomyopathy secondary to chronic incessant supraventricular tachycardia *Gladman, Wilkinson, and Evans-Jones* 402

Chronic neonatal Coxsackie myocarditis *Goren, Kaplan, Glaser, et al* 404

Regular review

Vesicoureteric reflux and renal scarring *White* 407

Personal practice

The management of squint *Fielder* 413

Contemporary history

Oral rehydration therapy: an epithelial transport success story *Greenough* 419

Neonatology—then and now *Walker* 423

Correspondence 424

Spring books

Book reviews 431

Report from the British Paediatric Surveillance Unit *Hall and Glickman* 439

BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

ISSN 0003–9888

ASTM CODEN: ADCHAK 64(3), 313–440, (1989)

Archives of Disease in Childhood

Editorial Committee

Editors: Bernard Valman and Malcolm Chiswick
Associate Editors: David Milner, Richard Robinson,
Michael Silverman, and Brian Wharton

D P Addy
A G M Campbell
M J Dillon
I M Hann
M J R Healy
I A Hughes
D I Johnston
J W Keeling
J V Leonard
J K Lloyd
S P Lock
N McIntosh
P J Milla
E R Moxon
P O D Pharoah
L Polnay
N Richman
L Spitz
M J Tarlow
J F N Taylor
R M Winter

Technical Editor: Sue Heels
Editorial Assistant: Jacinta Marshall

Notes to Contributors
Papers for publication should be sent to the Editors, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR and should be prepared in accordance with the 'Instructions to authors' published in the January and June issues of the journal. Copies of these instructions may be obtained from the editorial office on receipt of a stamped addressed envelope.

Notice to Advertisers
Applications for advertising space and rates should be made to the Advertisement Manager, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR.

Notice to Subscribers
Archives of Disease in Childhood is published monthly. The annual subscription rates are £98 inland and £115 overseas (USA $165). Orders should be sent to the Subscription Manager, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. (For the convenience of readers in the USA subscription orders, with or without payment, may also be sent to *British Medical Journal*, Box 560B, Kennebunkport, Maine 04046. All enquiries, however, must be addressed to the publisher in London.)

Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card.

All enquiries regarding air mail rates and single copies already published should be addressed to the publisher in London.

COPYRIGHT © 1989 by *Archives of Disease in Childhood.* This publication is copyright under the Berne Convention and the International Copyright Convention. All rights reserved. Apart from any relaxations permitted under national copyright laws, no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means without the prior permission of the copyright owners. Permission is not required to copy abstracts of papers or of articles on condition that a full reference to the source is shown. Multiple copying of the contents without permission is always illegal.

Second class postage paid, Rahway NJ. Postmaster: send address changes to: Archives of Disease in Childhood, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

Archives of Disease in Childhood, 1989, **64,** 313–316

Annotation

When to do a lumbar puncture in a neonate

Lumbar punctures or spinal taps are performed for either diagnostic or therapeutic reasons. The procedure in the neonate, however, is not without risk and the costs can outweigh the benefits. Stated indications for lumbar puncture range from routine sepsis work up to a more conservative approach reserving the procedure for the investigation of very ill babies. There is little consensus of opinion and no controlled trials comparing outcomes when different indications for lumbar puncture have been used.

Diagnostic use of lumbar puncture

MENINGITIS

It has been suggested that lumbar puncture should be performed as a routine before antibiotics are started in all babies with suspected sepsis.[1] There is, however, no agreement about what constitutes suspected sepsis, and some centres perform a lumbar puncture on all infants presenting with respiratory distress within 24 hours of birth.[2] Visser and Hall examined more than 500 concurrent blood and cerebrospinal fluid samples obtained from 400 infants with suspected sepsis admitted to their neonatal intensive care unit in Kansas City during a 12 month period.[1] Forty (7·8%) episodes of septicaemia or meningitis were found with organisms isolated from the blood in 39 cases and in only one infant was the cerebrospinal fluid culture positive when blood culture was negative. Only 11 (2·1%) babies had meningitis giving an incidence of meningitis in cases of septicaemia of 11 out of 40 (27·5%). Clinical findings and indications for culture did not distinguish those infants with positive blood or cerebrospinal fluid cultures from those with negative cultures, nor those with meningitis from those who had septicaemia without meningitis. In no cases were different organisms isolated from concurrent blood and cerebrospinal fluid cultures. On the face of it blood culture would appear to be as good as cerebrospinal fluid culture in obtaining the infecting organism during a screen for suspected sepsis.

The same authors, however, also looked at all their positive cerebrospinal fluid cultures over a six and one half year period.[1] They found 39 cases of meningitis based upon positive cultures but in only 33 babies (85%) was the organism also isolated from the blood. Thus in 15% of cases of meningitis the infecting organism would not have been identified by blood culture alone. This discrepancy between blood and cerebrospinal fluid culture was found in both early onset and late onset infections. Visser and Hall concluded that lumbar puncture should not be omitted from the routine assessment for infection in any neonate unless clinical judgment dictates that performance would cause dramatic and irreversible changes in the infant's condition.[1]

In contrast, Eldadah and colleagues reached a different conclusion after studying 238 consecutively admitted babies with respiratory distress syndrome.[2] Routine examination of cerebrospinal fluid in the first 24 hours of life failed to diagnose any case of meningitis in these babies. In 35 cases (14·7%) the lumbar puncture was unsuccessful and in 71 (29·8%) the cerebrospinal fluid was frankly bloody. In 17 babies concurrent blood cultures were positive. The authors conclude that in view of the negative cerebrospinal fluid examinations and the potential complications of lumbar puncture in the sick neonate that this procedure should not be routine in babies with respiratory distress syndrome. They suggest that lumbar puncture be reserved for babies who have additional risk factors such as hypothermia, hyperthermia, or poor feeding after 24 hours of age or for those babies with central nervous system signs such as coma or seizures.[2]

INTRACRANIAL HAEMORRHAGE

In 1979 it was stated that lumbar puncture was frequently required to diagnose meningitis or intracranial haemorrhage in the neonate.[3] With the development of computed tomography and later ultrasound imaging, however, this is no longer true and lumbar puncture is rarely used as a diagnostic aid for intraventricular haemorrhage. One study set out to compare lumbar puncture with computed tomography for the diagnosis of intracerebral haemorrhage in 48 babies of less than 35 weeks' gestation.[4] Computed tomography was performed at 48–96 hours and haemorrhage was present in 15 babies. Serial lumbar punctures were attempted with the initial procedure, which preceded the scan by one to four hours, and was successful in 28 (58·3%) babies. The first lumbar puncture was consistent with the scan diagnosis of haemorrhage in only eight of the 15 babies and in the other seven babies the initial tap was normal in three, traumatic in one, and unsuccessful in three. Furthermore, spinal taps showed bloody cerebrospinal fluid in 10 of 18 babies whose computed tomograms were normal.[4] The sensitivity of lumbar puncture in diagnosing intracranial haemorrhage was thus 73% and the specificity 44%.

For subarachnoid haemorrhage, however, lumbar puncture may be better than either computed tomography or ultrasound scan.[5] Cerebrospinal fluid protein values correlate quite well with the size of intraventricular haemorrhage on a computed tomogram.[6] Another possible advantage of lumbar puncture is the ability to time the onset of haemorrhage by comparing haemoglobin and bilirubin concentrations in cerebrospinal fluid using spectrophotometry.[7] This method will also distinguish traumatic tap and subarachnoid haemorrhage.

SEIZURES AND HYPOXIC-ISCHAEMIC ENCEPHALOPATHY

Several authorities have stated that a lumbar puncture is mandatory for the investigation of a newborn baby presenting with seizures or hypoxic-ischaemic encephalopathy.[8 9] The reasons given include the importance of determining opening pressure, and exclusion of intracranial haemorrhage and meningitis which may mimic hypoxic-ischaemic encephalopathy.[8 9] Some studies suggest that intracranial infection accounts for about 10% of neonatal seizures,[9 10] but in our experience neonatal meningitis is very rare with an incidence of only 0·5 per 1000 live births.[11]

Furthermore, onset of meningitis in the first week of life is very unusual and presentation with seizures alone even more uncommon.[11] In the investigation of seizures we would reserve lumbar puncture for ill babies or those in whom no obvious cause for the convulsion was present such as hypocalcaemia. We do not recommend lumbar puncture for the investigation of hypoxic-ischaemic encephalopathy without seizures unless there are other signs suggesting intracranial infection and the ultrasound scan is normal. It is possible that the measurement of creatine kinase brain isoenzyme concentration in the cerebrospinal fluid, however, provides a metabolic indicator of brain damage in newborns and this might justify the use of lumbar puncture to predict outcome of babies with hypoxic-ischaemic encephalopathy.[12]

Therapeutic use of lumbar puncture

MENINGITIS

Intrathecal instillation of antibiotics has been recommended for the treatment of meningitis in addition to systemic antibiotics as the latter are believed not to penetrate adequately in the cerebrospinal fluid. In a carefully controlled trial, however, McCracken and Mize found that intrathecal antibiotics given by lumbar puncture in association with systemic antibiotics were no more effective than intravenous antibiotics alone in treating neonatal meningitis.[13]

INTRACRANIAL HAEMORRHAGE

In 1980 Papile *et al* and Chaplin *et al* proposed that serial lumbar punctures were effective in arresting the progress of posthaemorrhagic hydrocephalus.[14 15] These studies were not controlled and did not take into account the natural history of posthaemorrhage hydrocephalus which may undergo spontaneous resolution.[16] A larger study of 48 babies failed to show that daily lumbar punctures prevented hydrocephalus after intraventricular haemorrhage,[6] and an accompanying editorial by Behrman called for a well controlled, short term, randomised study of serial lumbar puncture drainage of a substantial quantity of cerebrospinal fluid from a larger group of babies who are not subjected to any other unproved treatment at the same time.[17] Five years later Anwar *et al*, in a controlled study of 47 babies with either grade 3 or 4 intraventricular haemorrhage found that intermittent lumbar punctures were not effective in preventing posthaemorrhagic hydrocephalus.[18] At about the same time Kreusser *et al* using a Ladd monitor to measure intracranial pressure and ultrasound scanning suggested that two criteria were necessary before lumbar punctures could be effective in at least temporarily benefitting the baby with posthaemorrhagic hydrocephalus.[19] The first criterion was to show communication between the lateral ventricles and lumbar subarachnoid space by finding a reduction in ventricular size and a decrease in intracranial pressure after a removal of cerebrospinal fluid. The second criterion was to establish a critical volume of cerebrospinal fluid that must be removed, usually 10–20 ml before ventricular size and intracranial pressure were reduced.[19]

Repeated removal of cerebrospinal fluid in this fashion does have complications, notably hyponatraemia,[20] meningitis,[21] and epidural abscess with vertebral osteomyelitis[22] so that it should not be undertaken lightly and should only be performed in intensive care units that have ready access to ultrasound scanning and neurosurgical assistance. With current knowledge the efficacy of this treatment is not clear and further controlled studies are required.

Complications of lumbar puncture

The procedure, even in the smallest baby must be painful and uncomfortable and frequently causes clinical deterioration, which is more likely if both the head and legs are flexed.[23,24] One cause of the clinical deterioration is compression of the diaphragm during flexion rather than upper airway obstruction,[23] and this can be lessened by performing the lumbar puncture with the baby in either the sitting position or with neck extension rather than flexion.[23,24]

Traumatic tap and unsuccessful lumbar puncture are quite frequent occurrences in the neonate with only 45–54% being successfully completed.[2,3] The incidence of traumatic and unsuccessful lumbar puncture was similar whether a needle with a stylet, a butterfly needle without stylet, or a standard venepuncture needle without stylet were used.[3] Epidermoid spinal tumour has, however, been associated with the use of unstyletted lumbar puncture needles,[25,26] and these should probably be avoided when performing a lumbar puncture in the newborn.

As mentioned above repeated lumbar punctures for the treatment of posthaemorrhagic hydrocephalus have been associated with hyponatraemia,[20] meningitis,[21] and vertebral osteomylitis,[22] to which may be added local trauma to the skin of the back.

Conclusions

The indications for lumbar puncture in the newborn are not as clear cut as previously believed. Considerable doubt exists about whether they should be performed routinely in the baby with suspected sepsis or the ill baby with respiratory distress unless there are other pointers towards a diagnosis of meningitis. Reserving lumbar puncture only for the ill newborn will, however, increase the risks of clinical deterioration during and after the procedure, and of not obtaining a satisfactory sample of cerebrospinal fluid. Making a diagnosis of meningitis in a septicaemic baby will of course help with prognosis but is unlikely to aid treatment. As in the older child lumbar puncture can be delayed until the baby's condition is stable and treatment with high dose antibiotics has been allowed to have its effect.[27]

Lumbar puncture for diagnosis of intracranial haemorrhage is rarely needed after the introduction of bedside ultrasonic brain scanning. It should be reserved for the term infant with suspected subarachnoid haemorrhage where the diagnosis is uncertain clinically and the ultrasound scan is normal. Lumbar puncture need not be routine for investigation of seizures and hypoxic-ischaemic encephalopathy, and should be reserved for those ill babies in whom an alternative diagnosis of meningitis cannot be excluded on clinical or ultrasonic findings. The place of serial lumbar punctures for the management of posthaemorrhagic hydrocephalus remains to be clarified and larger controlled studies are needed.

I would like to thank my colleagues Drs Garth McClure and Mark Reid for their helpful comments and Lynda Thompson for typing the report.

References

[1] Visser VE, Hall RT. Lumbar puncture in the evaluation of suspected neonatal sepsis. *J Pediatr* 1980;**96**:1063–7.

[2] Eldadah M, Frenkel LD, Hiatt IM, Hegyi T. Evaluation of routine lumbar punctures in newborn infants with respiratory distress syndrome. *Pediatr Infect Dis J* 1987;**6**:243–5.

[3] Schreiner RL, Kleiman MB. Incidence and effect of traumatic lumbar puncture in the neonate. *Dev Med Child Neurol* 1979;**21**:483–7.

[4] Silverboard G, Lazzara A, Ahmann PA, Schwartz JF. Comparison of lumbar puncture with computed tomography scan as an indicator of intracerebral haemorrhage in the preterm infant. *Pediatrics* 1980;**66**:432–7.

[5] Shackelford GD, Volpe JJ. Cranial ultrasonography in the evaluation of neonatal intracranial haemorrhage and its complications. *J Perinat Med* 1985;**13**:293–304.

[6] Mantovani JF, Pasternak JF, Mathew OP, *et al.* Failure of daily lumbar punctures to prevent the development of hydrocephalus following intraventricular hemorrhage. *J Pediatr* 1980;**97**:278–81.

[7] Hellstrom B, Kjellin KG. The diagnostic value of spectrophotometry of the CSF in the newborn period. *Dev Med Child Neurol* 1971;**13**:789–97.

[8] Volpe JJ. Hypoxic-ischemic encephalopathy: clinical aspects. *Neurology of the newborn.* 2nd ed. Philadelphia: W B Saunders, 1987:236–79.

[9] Painter MJ, Bergman I, Crumrine P. Neonatal seizures. *Pediatr Clin North Am* 1986;**33**:91–109.

[10] Rose AL, Lombroso CT. A study of clinical, pathological and electroencephalographic features in 137 full-term babies with a long-term follow-up. *Pediatrics* 1970;**45**:404–25.

[11] Bell AH, Brown D, Halliday HL, McClure G, Reid M Mc. Meningitis in the newborn—a 14 year review. *Arch Dis Child* 1989 (in press).

[12] Worley G, Lipman B, Gewolb IH, *et al.* Creatine kinase brain isoenzyme: relationship of cerebrospinal fluid concentration to the neurologic condition of newborns and cellular localization in the human brain. *Pediatrics* 1985;**76**:15–21.

[13] McCracken GH Jr, Mize SG. A controlled study of intrathecal antibiotic therapy in Gram-negative enteric meningitis of infancy. Report of the neonatal meningitis cooperative study group. *J Pediatr* 1976;**89**:66–72.

[14] Papile L-A, Burstein J, Burstein R, Koffler H, Koops BL, Johnson JD. Posthemorrhagic hydrocephalus in low-birth-weight infants: treatment by serial lumbar punctures. *J Pediatr* 1980;**97**:273–7.

[15] Chaplin ER, Goldstein GW, Myerberg D, Hunt JV, Tooley WH. Post-hemorrhagic hydrocephalus in the preterm infant. *Pediatrics* 1980;**65**:901–9.

[16] Allan WC, Dransfield DA, Tito AM. Ventricular dilation following periventricular-intraventricular hemorrhage: outcome at age 1 year. *Pediatrics* 1984;**73**:158–62.

[17] Behrman RE. Serial lumbar punctures and intraventricular hemorrhage. *J Pediatr* 1980;**97**:250.

[18] Anwar M, Kadam S, Hiatt IM, Hegyi T. Serial lumbar punctures in prevention of post-hemorrhagic hydrocephalus in preterm infants. *J Pediatr* 1985;**107**:446–50.

[19] Kreusser KL, Tarby TJ, Kovnar E, Taylor DA, Hill A, Volpe JJ. Serial lumbar punctures for at least temporary amelioration

of neonatal posthemorrhagic hydrocephalus. *Pediatrics* 1985;**75**:719–24.

[20] MacMahon P, Cooke RW. Hyponatraemia caused by repeated cerebrospinal fluid drainage in post-haemorrhagic hydrocephalus. *Arch Dis Child* 1983;**58**:385–6.

[21] Smith KM, Deddish RB, Ogata ES. Meningitis associated with serial lumbar punctures and post-hemorrhagic hydrocephalus. *J Pediatr* 1986;**109**:1057–60.

[22] Bergman I, Wald ER, Meyer JD, Painter MJ. Epidural abscess and vertebral osteomyelitis following serial lumbar punctures. *Pediatrics* 1983;**72**:476–80.

[23] Weisman LE, Merenstein GB, Steenbarger JR. The effect of lumbar puncture position in sick neonates. *Am J Dis Child* 1983;**137**:1077–9.

[24] Gleason CA, Martin RJ, Anderson JV, *et al*. Optimal position for a spinal tap in preterm infants. *Pediatrics* 1983;**71**:31–5.

[25] Shaywitz BA. Epidermoid spinal cord tumors and previous lumbar punctures. *J Pediatr* 1972;**80**:638–40.

[26] Halcrow SJ, Crawford PJ, Craft AW. Epidermoid spinal cord tumour after lumbar puncture. *Arch Dis Child* 1985;**60**:978–9.

[27] Addy DP. When not to do a lumbar puncture. *Arch Dis Child* 1987;**62**:873–5.

H L HALLIDAY
Nuffield Department of Child Health,
Queen's University of Belfast,
Grosvenor Road, Belfast BT12 6BJ

Archives of Disease in Childhood, 1989, **64,** 317–320

Original articles

Penetrating eye injuries

B C K PATEL

Manchester Royal Eye Hospital

SUMMARY A review of all penetrating eye injuries treated at the Manchester Royal Eye Hospital over four years (1 January 1982–31 December 1985) was undertaken. A total of 202 penetrating eye injuries were seen of which 68 (34%) were in children under the age of 15 years. Airgun, dart, and knife injuries accounted for 28 (41%) of the injuries. Thirty seven patients (54%) achieved a good visual result (6/12 or better) and eight (12%) had enucleations. The period of inpatient treatment ranged from two to 18 days. From the analysis of the activities at the time of the injury, many of the injuries can be considered to be preventable.

Eye injuries are an important cause of visual disability in children.[1] [2] Penetrating eye injuries in children have a major impact in terms of long term morbidity and so are a matter of major socioeconomic importance. Prevention is of obvious importance but the causative factors must first be identified. Few studies have looked at the problem of penetrating eye injuries in children.

The purpose of this study was to analyse the causes, identify the types of injuries, and assess the visual outcome of penetrating eye injuries.

Patients and methods

The Manchester Royal Eye hospital is a 149 bed regional ophthalmic centre serving a population of approximately 1 million and has an annual accident and emergency department attendance of about 40 000 patients. Being a tertiary referral centre most penetrating eye injuries are referred to this hospital. We examined the records of all patients treated for penetrating eye injuries between 1 January 1982 and 31 December 1985. For patients aged 0–15 years details of the injuries including patient's age and sex, affected eye, activity at the time of injury, cause of the accident, extent of the injury, operative details, complications, and visual outcome were recorded. The total time spent as an inpatient was also noted.

Results

The total number of patients with penetrating eye injuries over the four year period was 202 (33 females and 169 males); of these 68 (34%) were children aged 0–15 years (56 boys and 12 girls). Table 1 shows the sex distribution by year and table 2 shows the age and sex distribution. There were 33 right and 35 left eyes involved. Injuries at school accounted for eight cases while the remainder

Table 1 *Annual distribution of penetrating eye injuries by sex*

Year	*Boys*	*Girls*	*Total*
1982	12	7	19
1983	14	1	15
1984	15	1	16
1985	15	3	18
Total	56	12	68

Table 2 *Age and sex distribution of penetrating eye injuries*

Age (years)	*Boys*	*Girls*	*Total*
<1	1	0	1
1	1	1	2
2	1	1	2
3	1	1	1
4	6	0	6
5	4	0	4
6	5	2	7
7	3	0	3
8	5	0	5
9	3	2	5
10	3	0	3
11	4	2	6
12	6	0	6
13	5	0	5
14	4	1	5
15	4	2	6
Total	56	12	68

occurred during leisure hours. Injury was caused by another child in 26 cases (38%).

The causes of the injuries are shown in table 3. The severity of the injury and the visual outcome is shown in table 4. Results are divided into four groups: good (6/12 or better), fair (6/18–6/36), poor (6/60-perception of light), and no perception of light. Airgun, dart, and knife injuries accounted for 28 (41%) of all penetrating injuries in children The details of the airgun and dart injuries are shown in tables 5 and 6. The length of inpatient treatment ranged from two to 18 days with a mean of 5·6 days. Of the eight eyes that were enucleated, three were enucleated because they were damaged beyond repair, one because of endophthalmitis, three for cosmetic reasons, and one because of absolute glaucoma. There were no cases of sympathetic ophthalmitis.

Table 3 *Causes of penetrating eye injuries (n=68)*

Cause		*No of injuries*
Darts		11
Glass		10
Knife		9
Airgun pellets		8
Stone		6
Twig		5
Bicycle		3
Sharp objects:		
Scissors	2	10
Compass	2	
Pen	2	
Fork	2	
Needle	1	
Coat hanger	1	
Miscellaneous:		
Radiator	1	3
Swing	1	
Hammering	1	
Unknown		3

Discussion

Children with eye injuries have been shown to make up 20%–29% of all ocular injuries requiring admission.[3 4] Penetrating eye injuries are the most important part of this group of patients as they result in the most severe visual disability.[5 6] Our ratio of boys to girls of 4·66:1 is similar to other studies.[4 7 8] Among the boys the incidence of injuries is maximum during the early school years and is very low below the age of 4.

The commonest causes of perforating eye injuries in children are pointed objects of various sorts.[1 2 5] In the present series they constituted 60%. Whereas explosives have accounted for some penetrating injuries in previous studies,[2 8] there were none in the present series.

Roper-Hall found that children below the age of 14 years made up 38% of patients with penetrating injuries over the period 1950 to 1958,[9] while the figure for Johnston was 28% between 1965 and 1969.[10] Our figure of 34% is in keeping with this.

Table 4 *Visual outcome for the four grades of injury (n=68)*

Extent of injury	*6/12 or better*	*6/18–6/60*	*6/60 or less*	*Enucleations*
Cornea with or without uvea	24	4	3	2
Cornea plus lens damage	5	8	4	1
Posterior segment injury with or without vitreous loss	5	1	1	1
Extensive anterior and posterior segment injury	1	1	1	4

Table 5 *Details of penetrating eye injuries caused by airgun pellets*

Age years	*Sex*	*Left or right eye*	*Circumstances*	*Visual acuity*
16	M	Left	Fired accidently by patient	6/9
14	M	Left	Walking in the park, fired at by unknown person	6/9
12	M	Right	Fired accidently by patient	Count fingers
15	M	Left	Fired accidently by brother	Perception of light
11	M	Right	Fired accidently by patient	6/5
16	M	Left	Fired accidently while cleaning	6/6
13	M	Right	Fired at by unknown person	6/60
10	M	Left	Fired accidently by patient	6/60

Table 6 *Details of injuries caused by darts*

Case No	*Age (years) Sex*	*Left or right eye*	*Circumstances*	*Injuries*	*Visual acuity*
1	6 F	Right	Dart thrown by brother	Corneal perforation, iris prolapse	6/9
2	6 F	Right	Pulling dart out of dartboard	Corneal perforation, iris prolapse	6/9
3	13 M	Right	Dart bounced off a surface	Scleral perforation, vitreous loss, retinal detachment	Count fingers
4	7 M	Left	Playing with a dart	Scleral perforation, vitreous loss, lens damage	Perception of light
5	3 M	Left	Dart thrown by friend	Corneal and scleral perforation	6/5
6	11 F	Left	Pulling dart out of dartboard	Corneal perforation, iris prolapse	6/6
7	5 M	Left	Playing with a dart	Corneal perforation, iris prolapse, lens damage	6/60
8	4 M	Left	Poked with a dart by brother	Corneal and scleral perforation, iridodialysis, retinal detachment	6/60
9	12 M	Left	Dart thrown by friend	Corneal perforation, iris prolapse	6/9
10	13 M	Left	Dart bounced off a surface	Corneal perforation, iris prolapse	6/9
11	9 M	Right	Playing with darts	Corneal perforation, iris prolapse	6/9

Johnston found that 20% of the children in his series had injured their eyes playing with toys such as arrows and catapults whereas the remainder were due to articles in and around the house such as sticks, knives, scissors, wire, glass, and fireworks. He pointed out that most parents' apparent lack of awareness of potential danger to their children's eyes was an important factor. In Roper-Hall's series, bow and arrow injuries were the most common cause accounting for 25%. Detailed analysis of the causes of injuries were not available in that series. Lambah found that over the 10 years 1951 to 1960, 163 penetrating injuries were seen in children and arrows accounted for 26, airgun injuries 12, miscellaneous pointed objects including knives accounted for 41, and assaults for 17.[8] The commonest causes in our series were darts (16%), knives (13%), and airgun pellets (12%). Miscellaneous sharp objects and glass related injuries each accounted for 15%.

In two major studies of penetrating eye injuries between 1950 and 1960 none were caused by darts.[8 9] In more recent studies in the 1970s and 1980s darts have been identified as a cause of penetrating injuries in children.[8 11] The game of darts was until recently an adult sport played largely in public houses. In recent years the sport has received extensive television coverage and has therefore become very popular. A survey of three large toy stores in London showed nine different types of darts on sale manufactured by three different companies. Only one company printed a clear warning on all its products. The warning reads 'Darts is an adult sport. It is dangerous for children to play without supervision'. Some of the other products carried warnings in small print while three had no warning at all. It is interesting to note that none of the penetrating eye injuries in adults were caused by darts.

Among children the biggest danger is at play and it would appear that parents' apparent lack of awareness of potential danger to their children's eyes is an important factor. There is at present no requirement for a physician to report ocular injuries caused by dangerous toys to the Consumer Safety Unit. The European Community directive on the safety of toys comes into effect on 1 January 1990 but darts with metallic points are excluded as they are not regarded as toys. It is suggested that all darts on sale should carry a clear and prominently displayed warning.

Prompt publicity by the media has previously proved to be very effective in preventing injuries caused by other toys.[9] The general public should be made aware of the vulnerability of children to injuries by darts. It may be argued that as the game of darts is recognised to be an adult sport darts and dartboards should not be sold in childrens' toy stores.

There have been several reports on penetrating eye injuries due to airgun pellets in recent years.[12] [13] A licence is not required for an airgun or air pistol but no person under the age of 17 years can purchase or hire one. No person under the age of 14 can accept as a gift or have in his possession an air weapon except when under the supervision of a person over 21 or when he is a member of an approved club or when the weapon is being used at a shooting gallery. Any person with a loaded air weapon in a public place is liable to imprisonment or a fine. Five of the eight patients injured by an airgun, however, were below 14 years of age. In five cases the accidents were due to careless handling of the airguns by the patient, in the remaining three cases the children had been fired at by assailants. The generally poor visual outcome of these injuries is not surprising. Although the law could be changed to provide further restrictions, this would probably not prevent children from handling such weapons and instruction of parents and children in schools may be of greater benefit. Eye injuries involving airguns are completely preventable and the emphasis should be on the fact that like darts, airguns are not toys.

Household items can be potentially dangerous and result in serious ocular injury when improperly handled by a child. A significant number of injuries resulted from play with items such as knives, glass bottles, scissors, compasses, and pens. In general, these injuries were more frequent in children less than 6 years of age. Parental supervision is vital to the prevention of such injuries and all potentially dangerous items should be removed from the reach of infants or toddlers. The use of plastic bottles would eliminate many potential hazards of breakage.

The Consumer Safety Unit of the Department of Trade and Industry has since 1976 collected information about accidents in the home that require attention in the accident and emergency departments of 20 hospitals in England and Wales. These do not at present include eye hospitals, however, and information on current causes of severe ocular trauma can only be obtained by studies carried out at major eye hospitals. This information is vital for the development of preventive measures. The reporting of the causes of all penetrating ocular injury to the Consumer Safety Unit would help to identify specific accident hazards.

References

[1] Niiranen M. Perforating eye injuries treated at Helsinki University Eye Hospital 1970 to 1977. *Ann Ophthalmol* 1981;**13:** 957–61.

[2] Werner S. On injuries to the eye in children. *Acta Ophthalmol (Copenh).* 1952;**30:**37–104.

[3] Maltzman BA, Pruzon H, Mund ML. A survey of ocular trauma. *Surv Ophthalmol* 1976;**21:**285–90.

[4] Grin TR, Nelson LB, Jeffers JB. Eye injuries in childhood. *Pediatrics* 1987;**80:**13–7.

[5] Sternberg P, De Juan E, Michels RG. Penetrating ocular injuries in young patients. Initial injuries and visual results. *Retina* 1984;**4:**5–8.

[6] Shock JP, Adams D. Long-term visual acuity results after penetrating and perforating ocular injuries. *Am J Ophthalmol* 1985;**100:**714–8.

[7] Niiranen M. Eye injuries in children. *Br J Ophthalmol* 1981;**65:** 436–8.

[8] Lambah P. Some common causes of eye injury in the young. *Lancet* 1962;**ii:**1351–3.

[9] Roper-Hall MJ. The treatment of ocular injuries. *Trans Ophthalmol Soc UK* 1959;**79:**57–69.

[10] Johnston S. Perforating eye injuries: a five year survey. *Trans Ophthalmol Soc UK* 1971;**91:**895–921.

[11] Eagling E. Perforating injuries of the eye. *Br J Ophthalmol* 1976;**60:**732–6.

[12] Bowen DI, Magauran DM. Ocular injuries caused by airgun pellets: an analysis of 105 cases. *Br Med J* 1973;**i:**333–7.

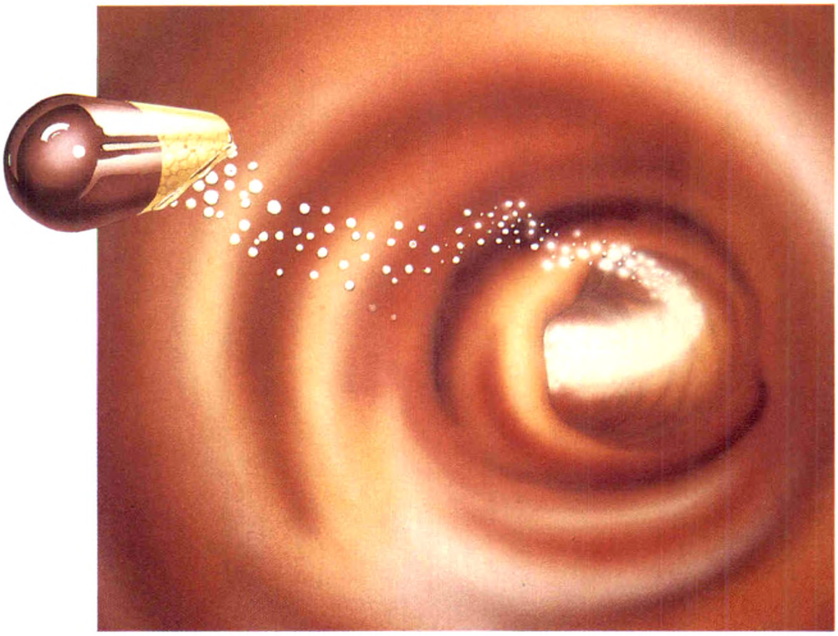
[13] Young DW, Little JM. Pellet-gun eye injuries. *Can J Ophthalmol* 1985;**20:**9–10.

Correspondence to Mr BCK Patel, Moorfields Eye Hospital, City Road, London EC1 2PD.

Accepted 18 July 1988

PROGRESS

In The Management Of Cystic Fibrosis



creon®

pancreatin

RIGHT ON TARGET – RIGHT FROM THE START

Prescribing Information – Presentation: Brown-yellow capsules containing enteric coated granules of pancreatin equivalent to: 9,000 BP units of amylase, 8,000 BP units of lipase, 210 BP units of protease. Available in packs of 100. Basic NHS price £13.33. **Indication:** Pancreatic exocrine insufficiency. **Dosage and administration:** Adults and children: Initially one or two capsules with meals, then adjust according to response. The capsules can be swallowed whole, or for ease of administration they may be opened and the granules taken with fluid or soft food, but without chewing. If the granules are mixed with food, it is important that they are taken immediately, otherwise dissolution of the enteric coating may result. **Contra-indications, Warnings, etc:** Contra-indications: Substitution with pancreatic enzymes is contra-indicated in the early stages of acute pancreatitis. Warnings: Use in pregnancy: There is inadequate evidence of safety in use during pregnancy. The product is of porcine origin. Rarely cases of hyper-uricosuria and hyper-uricaemia have been reported with high doses of pancreatin. Overdosage could precipitate meconium ileus equivalent. Perianal irritation could occur, and, rarely, inflammation when large doses are used. **Product Licence Number:** 5727/0001. **Name and address of Licence Holder:** Kali Chemie Pharma GmbH, Postfach 220, D-3000, Hannover 1, West Germany.

duphar Further information is available from:
Duphar Laboratories Limited, Gaters Hill, West End, Southampton SO3 3JD. Tel: 0703 472281.

CRAd/CF/1/89

Top this

Please send me more information on Phadiatop™

Name............................ Position............................

Address..

....

Return this coupon to:
Pharmacia Limited,
Pharmacia House,
Midsummer Boulevard
MK9 3HP.

In the diagnosis of inhalant allergy as a cause of respiratory symptoms, Phadiatop™

- is a simple laboratory test
- gives a yes/no answer
- is more than 95% accurate
- simplifies your diagnostic procedures
- helps in your patient management

Phadiatop™

THE YES/NO ANSWER IN INHALANT ALLERGY

Pharmacia

Pharmacia Limited, Pharmacia House,
Midsummer Boulevard, Milton Keynes, MK9 3HP.
Telephone 0908 661101.

Archives of Disease in Childhood, 1989, **64,** 321–325

Intestinal permeability in Crohn's disease

M S MURPHY,* E J EASTHAM,* R NELSON,* A D J PEARSON,* AND M F LAKER†

*Departments of *Child Health and †Clinical Biochemistry, University of Newcastle upon Tyne*

SUMMARY Crohn's disease may present insidiously, especially in childhood, and diagnosis may be delayed. In addition, the clinical assessment of the extent of disease activity may be inaccurate. Using mannitol and lactulose as probe molecules we have carried out a cross sectional study of intestinal permeability in patients with active Crohn's disease (n=17) and control subjects (n=31). Activity was assessed by an activity index score. The lactulose:mannitol urinary excretion ratio was significantly increased in Crohn's disease. Overall sensitivity was 82%, and 92% when activity was moderate or severe. When permeability was compared with the activity index there was a significant correlation among patients. In five patients studied longitudinally a significant correlation was also present. Measurement of intestinal permeability is non-invasive, and may be useful both as a screening test in patients with non-specific symptoms, and for the assessment of the extent of disease activity in patients with Crohn's disease.

The clinical onset of Crohn's disease is often insidious, with vague symptoms, and there may be a delay of several years before the definitive diagnosis is made.[1] A simple, non-invasive technique for use as a first line of investigation in children would be of considerable value in cases where suspicion is aroused. The clinical assessment of the extent of disease activity in Crohn's disease may be inaccurate,[2] and an objective measure of intestinal inflammation would be useful in management.

Abnormalities of intestinal permeability have been shown in children with various gastrointestinal diseases, including coeliac disease,[3] infective gastroenteritis,[4] and cystic fibrosis.[5] In a previous study, using mannitol and lactulose as probe molecules, we found abnormal permeability in a group of eight children with active Crohn's disease affecting the small bowel.[3]

In this paper we report the results of a further study of intestinal permeability in Crohn's disease in childhood. This was carried out to evaluate this technique further as a screening test for Crohn's disease. In addition we have compared the intestinal permeability in these children with an activity index score[2] to evaluate its potential for the assessment of the extent of disease activity.

Subjects and methods

Sugar permeability studies were performed in 17 patients (age range 6–16 years; 10 boys) in whom Crohn's disease had been diagnosed by conventional clinical, radiological, endoscopic, or histological criteria. In all cases the small bowel was affected. The results of the studies were compared with those obtained from 31 healthy children (age range 2–13 years; 18 boys).

The subjects were assessed by one of two paediatric gastroenterologists (EJE and RN) before the permeability studies were carried out, and a clinical judgment of the extent of disease activity was made; disease activity was graded subjectively as 'inactive', 'mild', 'moderate', or 'severe'. Simultaneously, using the criteria proposed by van Hees *et al*[2] the activity index score was calculated for each patient. The activity index is based on nine variables that include specific clinical observations, and also serum albumin concentration and erythrocyte sedimentation rate (mm in the first hour). This scoring system was designed to provide an objective and quantitative assessment of inflammatory activity in patients with Crohn's disease.

In addition to studying the group cross sectionally, four of the subjects were studied on two, and one on three, separate occasions to examine longitudinally the association between changes in inflammatory activity and intestinal permeability within individual patients.

After fasting overnight the subjects drank a test sugar solution containing 5 g mannitol and 5 g lactulose in 65 ml water (580 mmol/l). They continued to fast for a further two hours, but thereafter a liberal intake of fluids was encouraged to increase urine flow. Five hour urine collections were made and stored in containers to which 0·2 ml of sodium methiolate (0·1 g/l) had been added. The total volume was recorded and a 20 ml sample was separated and stored at −20°C. This was subsequently analysed by gas liquid chromatography by previously described methods.[6 7] The studies were carried out at home under parental supervision, unless the patient was in hospital.

The study was approved by the local ethics committee, and parents' informed consent was obtained. Results were analysed by the non-parametric Wilcoxon rank sum test, and Spearman's correlation coefficient.

Results

ACTIVITY OF CROHN'S DISEASE

At the time of the initial studies on the 17 patients four were judged clinically to have quiescent disease, but the activity index suggested that in three of these there was mild, and in one moderate, inflammatory activity. Of the 13 judged clinically to have active disease (one mild, six moderate, six severe), the activity index indicated that inflammatory activity was mild in one, moderate in seven, and severe in five. In fig 1 the extent of disease activity judged clinically is compared with that judged by the activity index at the time the permeability studies were carried out. This supports the view that simple clinical assessment may result in a lower estimate of the degree of inflammatory activity when compared with the more objective activity index.

INTESTINAL PERMEABILITY

The five hour urinary excretion of mannitol was not significantly different in the 17 subjects with Crohn's disease (range 5·9–21·3% of the ingested load, median 11·1%) compared with the control group (range 8·5–24·6%, median 13·2%), and only three patients had results below the normal range. Lactulose excretion, however, was significantly greater in those with Crohn's disease (range 0·2–2·6% of the

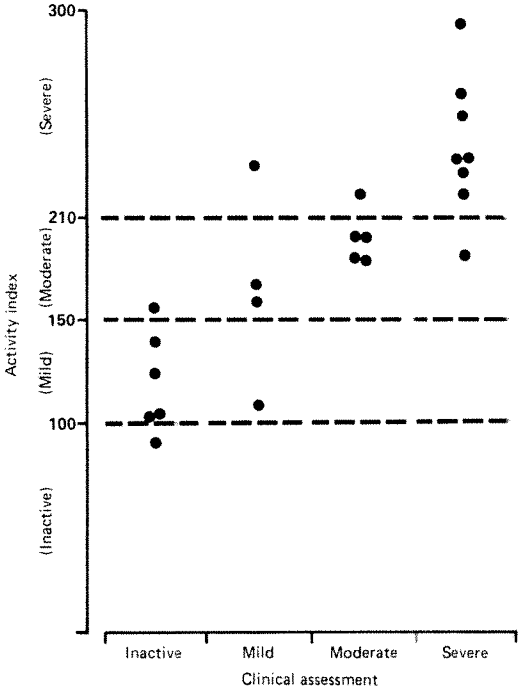


Fig 1 *Comparison of disease activity judged by clinical assessment, and by an activity index score.*[2]

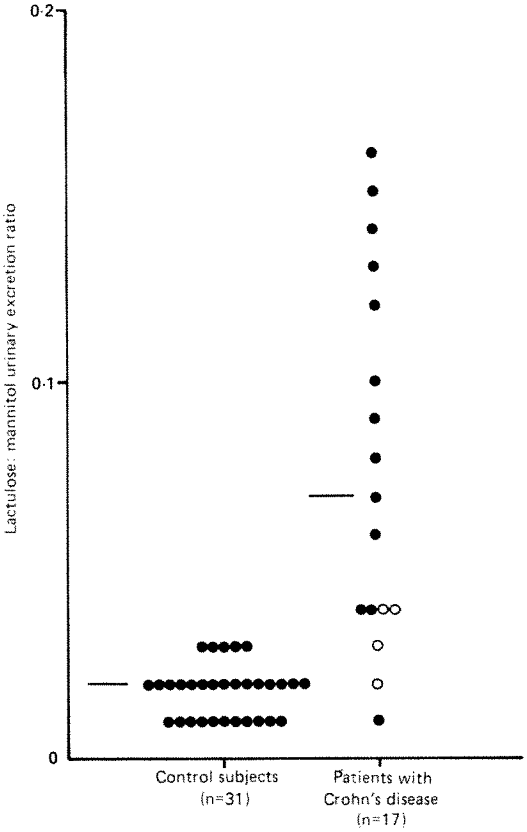


Fig 2 *Lactulose:mannitol urinary excretion ratio in control subjects and patients with Crohn's disease. Bars indicate median values. Activity index showed mild activity in four patients (open circles), and moderate or severe in the remainder.*

ingested load, median 0·67%) compared with the controls (range 0·1–0·66%, median 0·26%) (p<0·002), and 10 of the results were above the control maximum. The lactulose:mannitol excretion ratio was also significantly higher in those with Crohn's disease (range 0·01–0·16, median 0·07) compared with the controls (range 0·01–0·03, median 0·02) (p<0·0001), and using this index of permeability 14 were above the normal range (fig 2). The three patients whose lactulose:mannitol excretion excretion ratios were within the normal range (fig 2) were all thought clinically to have quiescent disease, although the activity index did suggest mild inflammatory activity in two and moderate activity in one.

CORRELATION BETWEEN PERMEABILITY AND DISEASE ACTIVITY

The correlation between the five hour urinary excretion of mannitol and the activity index was not significant (r_s=0·40; p=0·06). There was a moderately strong correlation, however, between lactulose excretion and the activity index (r_s=0·61; p<0·01) (fig 3), and also between the lactulose:mannitol ratio and the activity index (r_s=0·59; p<0·01) (fig 4). There was also a significant correlation between the changes in activity index and in the lactulose:mannitol excretion ratio within the small group of patients studied serially (r_s=0·83; p<0·05) (fig 5).

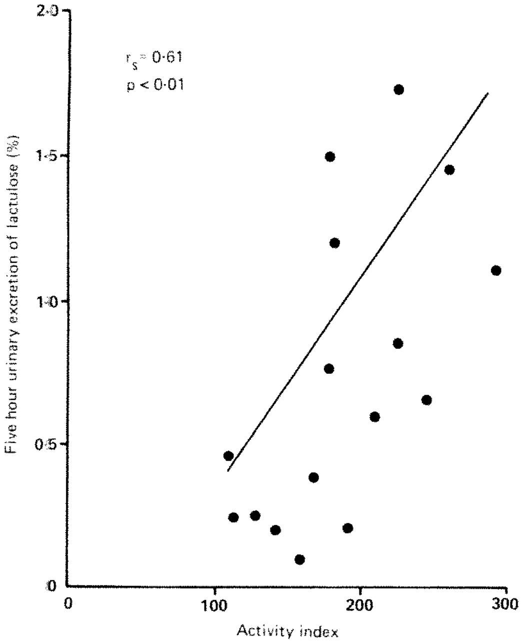


Fig 3 *Five hour urinary excretion of lactulose expressed as percentage of ingested dose compared with activity index.*

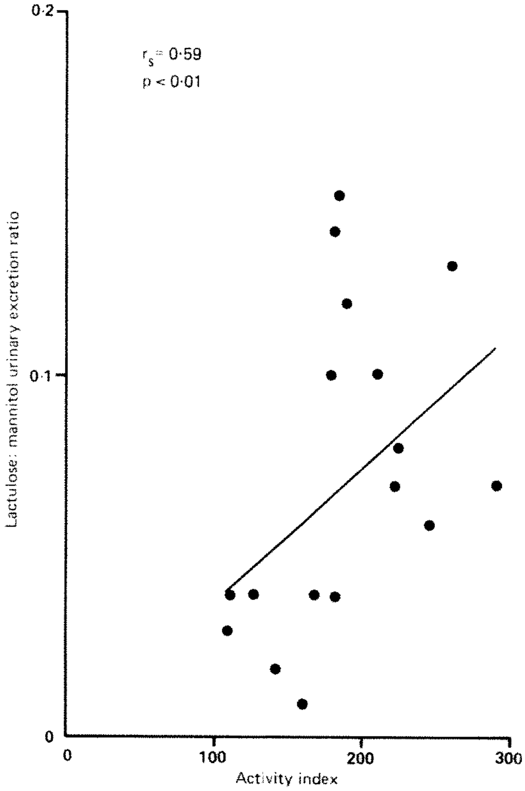


Fig 4 *Lactulose:mannitol urinary excretion ratio compared with activity index.*

Discussion

Contrast radiology, endoscopy, and histology are usually used to establish a definitive diagnosis of Crohn's disease. There is a natural reluctance, however, to subject patients to expensive, time consuming, and unpleasant procedures in pursuit of a comparatively rare disease, especially if the presenting symptoms are vague. In addition, these techniques sometimes fail to show the disease, particularly if it is confined to the small bowel, where radiological studies may be inconclusive and biopsy difficult. A prolonged delay in diagnosis is most likely to occur in patients with disease confined to the small bowel in whom the more specific symptoms of colitis are absent.[1]

Intestinal permeability indicates the capacity of the intestinal absorptive surface to permit passive

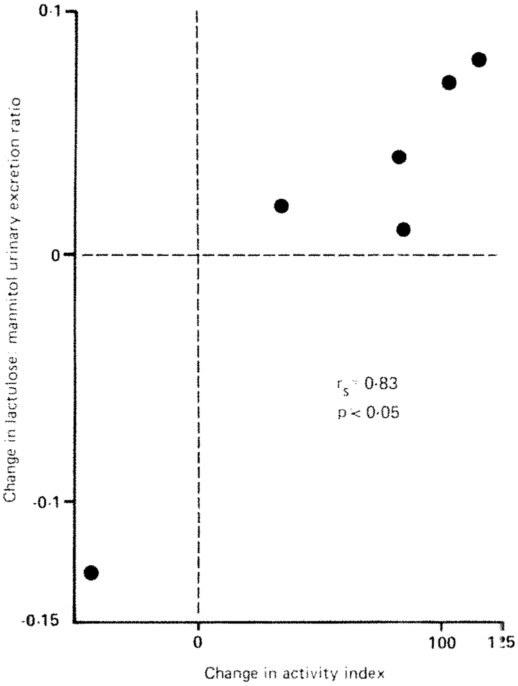


Fig 5 *Change in lactulose:mannitol urinary excretion ratio compared with the change in activity index score in patients studied longitudinally.*

penetration by water soluble molecules. It may be studied using orally administered probe molecules which are passively absorbed, are resistant to enzymatic digestion, are not metabolised, and are subject to quantitative renal excretion.[8] Measurement of the urinary excretion of such probes then provides a measure of intestinal absorption. In previous studies of intestinal permeability in Crohn's disease the following have been used: ^{51}Cr edetic acid,[9–11] polyethylene glycol (PEG 400),[12] and combinations of cellobiose and mannitol,[13] lactulose and mannitol,[3,14] or lactulose and l-rhamnose.[15] Together these studies have provided considerable evidence that the measurement of permeability may be a useful screening test for Crohn's disease if the small bowel is affected.

The use of a single probe molecule to assess intestinal permeability is complicated by the influence of factors other than the properties of the intestinal mucosa; gastrointestinal motility and renal function, for example, may affect absorption or excretion of the marker. By combining two probe molecules that are equally affected by such factors, the effects of these extraneous variables may be negated.[16] Mannitol, a polyhydric alcohol (molecular weight 182, radius 0·4 nm), is passively absorbed across the cell wall; lactulose, a synthetic disaccharide (molecular weight 342, radius 0·54 nm), seems to diffuse across the absorptive surface through intercellular pathways.[8] In diseases associated with mucosal damage and loss of enterocyte surface area, absorption of small probe molecules, such as mannitol, may be reduced, and absorption of disaccharides, such as lactulose, may be paradoxically enhanced as a consequence of increased 'leakiness' of the mucosal barrier. The expression of results as the lactulose:mannitol excretion ratio has proved a useful index of intestinal permeability that is sensitive to mucosal injury in patients with coeliac disease.[15] We have therefore preferred to use this technique in the study of Crohn's disease.

Although this study was carried out on subjects already known to have Crohn's disease, the results do provide further evidence that the measurement of intestinal permeability may be useful in the initial investigation of children in whom there is some suspicion of the disease. Only three of 17 children with Crohn's disease had lactulose:mannitol ratios within the normal range; these were all judged clinically to have inactive disease at the time of the study although the activity index did suggest mild activity in two and moderate activity in one. Interestingly, mannitol excretion was below the normal range in only three of the children, and lactulose excretion was above the normal range in only 10. These results support the use of a differential sugar absorption test, rather than a test based on the use of a single probe molecule in the study of patients with Crohn's disease. Using the lactulose:mannitol urinary excretion ratio as an index of permeability, the sensitivity of the test in detecting Crohn's disease associated with at least mild inflammatory activity as judged by the activity index was 82%, and in the presence of moderate to severe inflammatory activity this increased to 92%.

The increased intestinal uptake of lactulose in patients with coeliac disease compared with normal subjects is greatly enhanced when the test solution is extremely hypertonic (1500 mmol/l).[8] The test solution used in our studies was moderately hypertonic (580 mmol/l), and this was used as it was considered to be a palatable drink that was likely to be acceptable to young subjects. It is possible, however, that a more concentrated solution might (as in coeliac disease) further enhance the sensitivity of the test.

Crohn's disease has a variable course, and there is considerable difficulty in the clinical assessment of the extent of disease activity. For this reason several numerical indices of activity have been developed.[2,16,17] These have, however, not been completely satisfactory as they each have a subjective component and pronounced interobserver variation may occur.[18] A number of techniques have been introduced in recent years in an affort to develop a means of objective and non-invasive assessment of intestinal inflammation. Abdominal radioisotope scanning after the intravenous administration of ^{111}In or ^{99m}Tc labelled autologous phagocytes,[19–21] or the oral administration of ^{99m}Tc labelled sucralfate,[22] may show active Crohn's disease. Alternatively, faecal excretion of the isotope may be measured after intravenous administration of ^{111}In labelled phagocytes.[23] While these techniques may be of value in detecting active disease, their role in the evaluation of the extent of disease is less clear.

Gomes *et al*,[15] using the lactulose:rhamnose excretion ratio, reported that intestinal permeability is abnormal in patients with active Crohn's disease but returns to normal when they enter remission. Our cross sectional study showed a correlation with intestinal inflammatory activity between individual patients; in addition in five patients studied longitudinally there was also a correlation with inflammatory activity within individuals. This technique may therefore have a useful role in the assessment of the extent of disease activity. To evaluate this further, studies to examine the association between intestinal permeability and the findings on endoscopic and radiological investigation are needed.

References

[1] Gryboski JD, Spiro HM. Prognosis in children with Crohn's disease. *Gastroenterology* 1978;**74**:807–17.

[2] van Hees PAM, van Elteren, van Lier HJJ, van Tongeren JHM. An index of inflammatory activity in patients with Crohn's disease. *Gut* 1980;**21**:279–86.

[3] Pearson ADJ, Eastham EJ, Laker MF, Craft AW, Nelson R. Intestinal permeability in children with Crohn's disease and coeliac disease. *Br Med J* 1982;**285**:20–1.

[4] Ford RPK, Menzies IS, Phillips AD, Walker-Smith JA, Turner MW. Intestinal sugar permeability: relationship to diarrhoeal disease and small bowel morphology. *J Pediatr Gastroenterol Nutr* 1985;**4**:568–74.

[5] Leclercq-Foucart J, Forget PP, Van Cutsem JL. Lactulose-rhamnose intestinal permeability in children with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1987;**6**:66–70.

[6] Laker MF. Estimation of disaccharides in plasma and urine by gas-liquid chromatography. *J Chromatogr* 1979;**163**:9–18.

[7] Laker MF, Mount JN. Mannitol estimation in biological fluids by gas-liquid chromatography. *Clin Chem* 1980;**26**:441–3.

[8] Menzies IS. Transmucosal passage of inert molecules in health and disease. In: Skadhauge E, Heintze K, eds. *Falk symposium 36. Intestinal absorption and secretion*. Lancaster: MTP Press, 1984:527–43.

[9] Bjarnason I, O'Morain C, Levi AJ, Peters TJ. Absorption of ^{51}chromium labelled ethylene diamine tetraacetate in inflammatory bowel disease. *Gastroenterology* 1983;**85**:318–22.

[10] Peled Y, Watz C, Gilat T. Measurement of intestinal permeability using ^{51}Cr-EDTA. *Am J Gastroenterol* 1985;**80**:770–3.

[11] O'Morain CA, Abelow AC, Chervu LR, Fleischner GM, Das KM. Chromium 51-ethylenediaminetetraacetate test: a useful test in the assessment of inflammatory bowel disease. *J Lab Clin Med* 1986;**108**:430–5.

[12] Hollander D, Vadheim CM, Brettholz E, Petersem GM, Delahunty T, Rotter JI. Increased intestinal permeability in patients with Crohn's disease and their relatives. A possible etiologic factor. *Ann Intern Med* 1986;**105**:883–5.

[13] Cobden I, Rothwell J, Axon ATR. Intestinal permeability and screening tests for coeliac disease. *Gut* 1980;**21**:512–8.

[14] Ukabam SO, Clamp JR, Cooper BT. Abnormal small intestinal permeability to sugars in patients with Crohn's disease of the terminal ileum and colon. *Digestion* 1982;**27**:70–4.

[15] Gomes M De Fa, Dunne J, Logan LH, Pounder RE. Non-invasive assessment of small intestinal damage in Crohn's disease and ulcerative colitis. *Gut* 1983;**24**:A486.

[16] Cobden I, Dickenson RJ, Axon ATR. Intestinal permeability assessed by excretion ratios of two molecules: results in coeliac disease. *Br Med J* 1978;**i**:1060.

[17] Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. *Gastroenterology* 1976;**70**:439–44.

[18] Harvey RF, Bradshaw JM. A simple index of Crohn's disease activity. *Lancet* 1980;**i**:514.

[19] De Dombal FT, Softley A. IOIBD report no 1: observer variation in calculating indices of severity and activity in Crohn's disease. *Gut* 1987;**28**:474–81.

[20] Saverymuttu SH, Lavender JP, Hodgson HJF, Chadwick VS. Assessment of disease activity in inflammatory bowel disease: a new approach using ^{111}In granulocyte scanning. *Br Med J* 1983;**287**:1751–3.

[21] Leddin DJ, Paterson WG, DaCosta LR, *et al*. Indium-111-labelled autologous leukocyte imaging and fecal excretion. Comparison with conventional methods of assessment of inflammatory bowel disease. *Dig Dis Sci* 1987;**32**:377–87.

[22] Pullman W, Hanna R, Sullivan P, Booth JA, Lomas F, Doe WF. Technetium-99m autologous phagocyte scanning: a new imaging technique for inflammatory bowel disease. *Br Med J* 1986;**293**:171–4.

[23] Dawson DJ, Khan AN, Miller V, Ratcliffe JF, Shreeve DR. Detection of inflammatory bowel disease in adults and children: evaluation of a new isotopic technique. *Br Med J* 1985;**291**:1227–30.

Correspondence to Dr M S Murphy, Division of Pediatric Gastroenterology and Nutrition, The Children's Hospital, 300 Longwood Avenue, Boston, Massachusetts 02115, USA.

Accepted 10 August 1988

Archives of Disease in Childhood, 1989, **64,** 326–329

Campylobacter pylori gastritis: long term results of treatment with amoxycillin

G ODERDA,* D DELL'OLIO,* I MORRA,† AND N ANSALDI*

**Gastroenterology Service, Department of Paediatrics, University of Turin, and †Pathology Department, Children's Hospital Regina Margherita, Turin, Italy*

SUMMARY To evaluate the efficacy of amoxycillin in eradicating *Campylobacter pylori,* endoscopic biopsy specimens were taken from the antral mucosa of 40 children with gastritis before, immediately after, and (in 30 patients) three months after treatment. Immediately after treatment 34 patients (85%) no longer had the organism in the mucosa, and the gastritis had healed in 23 (58%). Three months later the infection had recurred in 22 of 30 patients (73%), and the gastritis had relapsed in all of them. Significantly more children in whom *C pylori* recurred had family histories of peptic ulcer disease. The results suggest that amoxycillin alone is ineffective in the long term treatment of *C pylori* gastritis.

Since the description by Warren and Marshall of S shaped spiral Gram negative bacteria in the antral mucosa of adult patients with gastritis or peptic ulcer,[1] the association between *Campylobacter pylori* and gastritis has also been described in children,[2 3] and the incidence among children undergoing endoscopy for upper gastrointestinal symptoms varies between 20 and 24%.[4 5] Though the relationship has not been proved to be causal, preliminary studies have shown that elimination of the organism results in improvement or healing of the gastritis,[6] thereby providing indirect evidence of its pathogenic role. Eradication has been achieved in adults with courses of amoxycillin,[6] or tripotassium dicitratobismuthate,[7] or a combination of the two, but relapse is common.

The aim of this study was to evaluate the efficacy of amoxycillin in the eradication of *C pylori* and the resolution of the peptic mucosal lesions in children with gastritis both immediately after the course of treatment, and three months later.

Patients and methods

Forty two children who had had *C pylori* isolated from the gastric mucosa were entered into the study between March 1987 and February 1988 (table 1). Fifteen of the children had undergone upper gastrointestinal endoscopy for recurrent abdominal pain (with or without vomiting) of six months to five years' duration; the remainder had the examination as part of their follow up after treatment for peptic ulcer or reflux oesophagitis. Those with peptic ulcers had all been treated with ranitidine, and all but one were free of symptoms: those with reflux oesophagitis had been treated with antacids and all were free of symptoms.

Endoscopy was carried out with a paediatric gastroscope (Olympus GIF P3 or GIF XP20) after an overnight fast. Patients were sedated with oral diazepam and their throats were anaesthetised with amethocaine. Three biopsy specimens were taken from the antral mucosa within 1 cm from the pylorus. One was inserted into a rapid urease test (CLO-test, Delta West),[8] one was put into chocolate agar medium for microaerobic culture, and the third

Table 1 *Clinical details of 42 patients at presentation. Figures given are number of patients except for age*

Age (years):	
Mean (SD)	12·2 (2·6)
Range	8–18
Sex (male:female)	26:16
Symptoms:	
Recurrent abdominal pain	16
Vomiting	7
Nausea	2
Anorexia	1
Haematemesis	1
Indication for endoscopy:	
Recurrent abdominal pain	15
History of peptic disease	18
Healing ulcer	17
Exacerbation of symptoms	1
History of oesophagitis	9

was cut into sections and stained with haematoxylin and eosin for histological examination, and Giemsa stain for identification of *C pylori*. Antral gastritis was defined according to the criteria of Whitehead *et al*[9]: a diffuse chronic inflammatory cell infiltration of the lamina propria was considered to be quiescent chronic superficial gastritis, and if neutrophils were present within the superficial or glandular epithelium, or both, it was considered to be active chronic superficial gastritis. Atrophic changes in the glandular epithelium were not found.

Treatment with amoxycillin 25 mg/kg twice daily was started as soon as colonisation by *C pylori* had been confirmed either by the CLO-test or on the Giemsa stained biopsy specimen, and continued for four weeks. In addition the nine patients who had had reflux oesophagitis continued postural treatment, and six children who had had relapses of their symptoms of peptic ulceration continued to take maintenance doses of ranitidine (2·5 mg/kg at bedtime). Patients were also allowed to take antacids if necessary.

The morning after the course of amoxycillin had finished the children were endoscoped again, and if *C pylori* had been eradicated no further treatment was given and they were asked to return three months later for further endoscopy. If *C pylori* was still present treatment with other drugs was started. At each endoscopy the presence of *C pylori* was assessed both by CLO-test and by Giemsa staining of an antral biopsy specimen.

To see if there were any differences between children in whom *C pylori* recurred and those in whom it did not, details of history, age, sex, family history of peptic ulcer disease, duration of symptoms, activity of the gastritis, and the pattern of the antrum at endoscopy were recorded.

Unpaired data were compared by the χ^2 test with Yates's correction and paired data by McNemar's test; ordinal data were compared by Student's *t* test. A p value of $<0·05$ was accepted as significant. There is no ethical committee in our hospital, but it is our practice to inform parents and children fully about every procedure and to obtain consent even for the most routine measures.

Results

C pylori was identified by Giemsa staining of antral biopsy specimens in all 42 children. The CLO-test was positive in 38 (90%), and *C pylori* was grown on culture in 34 (81%). Endoscopic and histological findings are summarised in table 2.

Forty of the 42 children had the endoscopy repeated immediately after the course of amoxycillin (two refused). Giemsa staining of antral biopsy specimens showed that in 34 children *C pylori* had been eradicated (85%, $p<0·001$); the CLO-test was negative in all of them. Two children complained of recurrent abdominal pain, although it was less severe, but in the remainder it had resolved in a mean (SD) of 15 (9) days. No other symptoms were reported. In six children Giemsa staining of the antral biopsy specimens showed that *C pylori* was still present, and the CLO-test was positive in four of these. In one of these the recurrent abdominal pain was worse, but the others were free of symptoms.

Thirty of the 34 children in whom *C pylori* had

Table 2 *Endoscopic and histological findings*

	Before treatment started	*Immediately after treatment stopped*		*Three months after treatment stopped*	
		C pylori not present	*C pylori present*	*C pylori not present*	*C pylori present*
No of children	42	34	6	8	22
Endoscopic findings:					
Normal antrum	—	18	—	4	8
Nodular antritis	23	7	2	1	9
Pyloric hyperaemia	19	9	4	3	5
Oesophagitis	8	7	—	2	3
Duodenitis	6	2	—	—	1
Duodenal ulcer	1	—	—	—	2
Histological findings:					
Normal antrum	—	23	—	8	—
Chronic superficial gastritis:					
Quiescent	26	9	4	—	9
Active	16	2	2	—	13
Oesophagitis	11	4	—	1	—
Duodenitis	6	1	—	1	2

been eradicated immediately after the course of treatment had further endoscopies three months later. In 22 of these Giemsa staining of antral biopsy specimens showed that *C pylori* had recurred (73%, $p<0·001$); the CLO-test was positive in 19. Two of the children developed recurrent abdominal pain about two months after the course of amoxycillin, but the pain was less severe than it had been at presentation and there were no associated symptoms. In eight children the *C pylori* did not recur and the CLO-test was negative in all eight. One of these developed mild recurrent abdominal pain about a month after treatment had been stopped.

There were no significant differences between the 22 children in whom *C pylori* recurred and the eight in whom it did not except in the incidence of a family history of peptic ulcer disease; all the children who had a recurrence had a family history of peptic ulcer compared with two of the eight who did not ($p<0·001$).

Discussion

The prevalence of *C pylori* infection in children is lower than in adults, and increases with age.[10] In children with gastritis, however, it is similar to that in adults with peptic ulcer disease and varies from 70[11] to 80%.[12]

The endoscopic picture of the gastric antrum in children with gastritis associated with *C pylori* has been described as nodular[13]; in a retrospective study of 31 children with nodular antral gastritis we found *C pylori* in 90%,[14] but this is not the only picture found in gastritis associated with *C pylori*. In the present series nodular antral gastritis was found in only 23 (55%) of children before treatment. In the rest there was only mild hyperaemia of the pylorus, a nearly normal picture. If the antrum is nodular, therefore, *C pylori* should be sought, but other findings do not exclude its presence. Macroscopically normal mucosa may be histologically abnormal both in children and adults, but a nodular antrum is not predictive of a higher recurrence rate. There was a good correlation between the presence of *C pylori* and gastritis, but signs of active gastritis were not predictive of recurrent infection.

C pylori can also be associated with oesophagitis,[15] and in the present series histological changes typical of peptic oesophagitis (lengthening of the papillae, inflammatory infiltration of the epithelium, and thickening of the basal layer) were more common than macroscopic oesophagitis at endoscopy. We treated these children even if they had no symptoms, because traditional treatment had failed to heal the histological damage of the mucosa that looked normal at endoscopy: our results suggest that eradication of *C pylori* is associated with the healing of oesophagitis.

Seventeen of the 18 children who had histories of peptic ulcer disease were free of symptoms, but we elected to treat them because we hoped to do them good by eradicating *C pylori*. In a long term follow up study of children with peptic ulcers[16] we found that 89% of those with relapsing peptic ulcer disease were carriers of *C pylori*, compared with 29% of those in whom it did not relapse. In the present series one child had a duodenal ulcer that healed after the course of amoxycillin, and in two others ulcers relapsed when the *C pylori* infection recurred three months later. Longer periods of follow up and larger series of patients are needed to confirm these data.

Though symptoms that were present before treatment disappeared within a fortnight in most cases, the response to amoxycillin was not predictive of recurrence of *C pylori*. Mild abdominal pain recurred in three children in whom *C pylori* had recurred (13%) and in one in whom it had not (12%).

From these data it seems that upper gastrointestinal endoscopy is the only way of proving that *C pylori* is present in the stomach, but to do the endoscopy immediately after treatment is useless as it will not show whether long term eradication of the organism has been achieved.

Amoxycillin alone does not seem to be effective in the long term eradication of *C pylori*; we had planned to enrol more patients in the study but because of the unacceptably high recurrence rate (73%) we did not feel justified in doing so. It seems likely that treatment with combinations of drugs—for example, amoxycillin with tripotassium dicitratobismuthate or metronidazole, or both[17]—may be necessary to eradicate the organism entirely. The six children from whose stomachs *C pylori* was isolated at the first follow up, and the 22 in whom it had recurred at three months, were treated with combinations of drugs.

Whether recurrence of *C pylori* infection is caused by relapse, or reinfection by exogenous strains, is not certain but the significantly higher incidence of recurrence among those children with family histories of peptic ulcer disease suggests that reinfection from contacts in the families may be the cause. Long term eradication may be better effected by treatment of all infected family members.

We thank the Cassa di Risparmio di Torino for the donation that enabled us to buy our endoscopes.

References

[1] Warren JR, Marshall BJ. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983;i:1273–5.

[2] Cadranel S, Goossens H, De Boeck M, Malengreau A, Rodesch P, Butzler J. Campylobacter pyloridis in children. *Lancet* 1986;**i**:735–6.

[3] Drumm B, O'Brien A, Cutz E, Sherman P. Campylobacter pyloridis-associated primary gastritis in children. *Pediatrics* 1987;**80**:192–5.

[4] Eastham EJ, Elliott SM. Campylobacter pyloridis in children. *Arch Dis Child* 1987;**62**:652.

[5] Mahony MS, Wyatt J, Littlewood JM. Campylobacter associated gastritis in children. *Gut* 1987;**28**:A1357.

[6] Rauws EAJ, Langenberg W, Houthoff HJ, Zanen HC, Tytgat G. Campylobacter pyloridis-associated chronic active antral gastritis. *Gastroenterology* 1988;**94**:33–40.

[7] McNulty CAM, Gearty JC, Crump B, *et al.* Campylobacter pyloridis and associated gastritis: investigator blind, placebo controlled trial of bismuth salicylate and erythromicin ethylsuccinate. *Br Med J* 1986;**293**:645–9.

[8] Morris A, McIntyre D, Rose T, Nicholson G. Rapid diagnosis of Campylobacter pyloridis infection. *Lancet* 1986;**i**:149.

[9] Whitehead R, Truelove SC, Gear MWL. The histological diagnosis of chronic gastritis in fiberoptic gastroscope biopsy specimens. *J Clin Pathol* 1972;**25**:1–11.

[10] Berkowicz J, Lee A. Person-to-person transmission of Campylobacter pylori. *Lancet* 1987;**ii**:680–1.

[11] Drumm B, Sherman P, Cutz E, Karmali M. Association of Campylobacter pylori on the gastric mucosa with antral gastritis in children. *N Engl J Med* 1987;**316**:1557–61.

[12] Mahony MJ, Wyatt JI, Littlewood JM. Campylobacter pylori gastritis. *Arch Dis Child* 1988;**63**:654–5.

[13] Czinn SJ, Dahms BB, Jacobs GH, Kaplan B, Rothstein FC. Campylobacter-like organisms in association with symptomatic gastritis in children. *J Pediatr* 1986;**109**:80–3.

[14] Oderda G, Lerro P, Poli E, Tavassoli K. Childhood nodular antritis and Campylobacter pylori. *Endoscopy* 1988;**20**:86.

[15] Borkent MV, Beker JA. Treatment of ulcerative reflux oesophagitis with colloid bismuth subcitrate in combination with cimetidine. *Gut* 1988;**29**:385–9.

[16] Oderda G, Ansaldi N. Peptic ulcer in childhood. *Lancet* 1988;**i**:302–3.

[17] Borsch G, Mai U, Opferkuch W. Oral triple therapy may effectively eradicate Campylobacter pylori in man. A pilot study. *Gastroenterology* 1988;**94**:A44.

[18] Oderda G, Boero M, Ponzetto A, Bellis D, Ansaldi N. Campylobacter pylori in families of children with relapsing gastroduodenal disease due to C pylori, *Am J Gastroenterol* 1988;**83**:134–8.

Correspondence to Dr G Oderda, Gastroenterology Service, University of Turin, Piazza Polonia 94, 10126 Torino, Italy.

Accepted 18 October 1988

Archives of Disease in Childhood, 1989, **64,** 330–332

Coarctation of the aorta corrected during the first month of life

P EHRHARDT AND D R WALKER

Killingbeck Hospital, Leeds

SUMMARY Forty eight children (29 boys) had surgical correction of coarctation of the aorta during the first month of life; all had patent ductus arteriosus. The 33 survivors were reviewed at a mean age of 6·6 years. Of the 19 children with no associated anomaly, none had died. The more complex the associated anomalies, the greater the mortality. Two (6%) of the survivors, both with associated anomalies, have some residual disability; one is incapable of leading an independent life. No survivor has systemic hypertension. Six (18%) of the survivors have required correction of recurrent coarctation, and one is awaiting repair.

Newborn babies suspected of having coarctation should be assessed for surgical correction without delay, and medical treatment (including, if necessary, infusion of prostaglandin E_2 in a dose of 0·025 μg/kg/minute) should be instituted in the interim. Long term follow up is important to detect systemic hypertension or recurrence of the coarctation. This occurred in seven (21%) of our survivors.

Coarctation of the aorta presenting in the neonatal period, with or without associated anomalies, is a life threatening condition, and the prognosis is poor if surgical correction is not carried out. Recent advances in medical management, in particular infusion of prostaglandin E_2, permit such babies to be stabilised in better condition before operation. Despite such advances, however, many babies arrive in the cardiothoracic surgical unit with severe complications—for example, cardiac failure, hypoxia, acidaemia, shock, renal failure, or septicaemia.

The immediate results of surgical correction have been reported from a number of centres including our own.[1-4] Potential long term complications include recurrence of the coarctation, the effects of any coexisting anomalies, the consequences of any perioperative problems, and the development of systemic hypertension.

We present our results in 48 consecutive babies with coarctation of the thoracic aorta who underwent surgical correction during the first month of life and were reviewed in childhood.

Methods

Correction of coarctation of the aorta was carried out in 48 babies aged 1 month or less between March 1978 and April 1982. Subclavian flap correction[5] was carried out in 45 children, each of the remaining three having a polytetrafluoroethylene patch prosthesis inserted. All 48 children had patent ductus arteriosus.

For the purposes of this study we allotted the children to one of three groups according to the severity of their coexisting anomalies. The first group had no associated intracardiac lesion, the second group had associated ventricular septal defects, and the third group had more complicated anomalies.

At follow up the children were assessed according to recurrence of the coarctation, the development of systemic hypertension, their general physical health, and any evidence of handicap.

Results

The clinical features of the 48 babies are shown in the table. There were 29 boys and 19 girls, and all had patent ductus arteriosus.

BABIES WITH NO INTRACARDIAC ANOMALY

Twelve boys and seven girls had no other anomaly; their gestational ages ranged from 36 weeks to 41 weeks 3 days, and their birth weights from 2290 g to 3540 g. There were no deaths in this group, and they

Table *Features of 48 babies with coarctation of the aorta operated on during the first month of life.*

	Associated anomalies		
	None	*Ventricular septal defect*	*More complex anomalies*
Total No	19	15	14
Sex (male:female)	12:7	8:7	9:5
Mean (SD) birth weight (g)	3050 (360)	2770 (680)	3380 (680)
Mean (SD) gestational age (weeks)	39·2 (1·8)	38·1 (2·2)	40·6 (1·2)
Mean (SD) age at operation (days)	14·2 (7·6)	10·3 (6·5)	12·0 (6·7)
No of early deaths	0	5	5
No of late deaths	0	0	5
No of survivors	19	10	4
Sex (male:female)	12:7	5:5	2:2
Mean (SD) age at follow up (years)	6·70 (1·47)	5·96 (1·15)	7·45 (0·95)
No of recurrences of coarctation	8*	1	1†
Mean (SD) systolic blood pressure (mm Hg)	117 (15)	101 (17)	103 (9)
Mean (SD) diastolic blood pressure (mm Hg)	70 (8)	60 (6)	64 (10)
Disability	0	1	1

*Coarctation recurred twice in one boy and one girl; †this boy, with a single ventricle, had second repair when 11 months old and died at the age of 13 months.

were reviewed at a mean age of 6·7 years (range 4·6 to 9·3).

Four children required a second correction of coarctation at the ages of 1·3 years, 2·4 years, 4·4 years, and 6·4 years, respectively. The first and third of these children each required a third correction at the ages of 8·1 years and 6·5 years, respectively, and one further child awaits correction of a recurrence at the age of 6·2 years.

Apart from the child who is waiting for correction of a recurrence no child has a disability in this group. All the children are in good physical health without systemic hypertension, and are developing normally.

BABIES WITH AN ASSOCIATED VENTRICULAR SEPTAL DEFECT

Eight boys and seven girls had only an associated ventricular septal defect. Their gestational ages ranged from 33 to 40 weeks, and birth weights from 1720 g to 4010 g. Five babies (33%) died between one and 28 days postoperatively, three in 1978 before the introduction of prostaglandin E_2 infusion to improve their preoperative condition.

One child (7% of the original group), a girl of 6·4 years, is disabled. She weighed 2800 g at term, and was acidaemic and severely ill when she presented. Postoperatively she had several seizures. She had a renal vein thrombosis leading to chronic renal failure, and has failed to thrive. She is now being considered for a renal transplant, and attends a school for children with learning difficulties.

The remaining nine children (60% of the original group) are well at a mean age of 5·9 years (range 3·8 to 7·4) and are developing normally. One girl required correction of a recurrent coarctation at the age of 3 months. None of the 10 survivors has systemic hypertension or further recurrence of the coarctation, and none has required an operation for the ventricular septal defect.

BABIES WITH MORE COMPLEX ASSOCIATED ANOMALIES

Nine boys and five girls had more complex associated anomalies. Their gestational ages ranged from 38 to 43 weeks, and their birth weights from 2400 g to 4800 g. Five babies (36%) died between five and 28 days postoperatively. All were expected to require eventual intracardiac repair. Five (36%) died between the ages of 3 months and 3·2 years. In each case, intracardiac repair had either been undertaken or was planned. There were four survivors (29%).

One boy aged 7·5 years with aortic stenosis weighed 3790 g when he was born at full term. He required treatment with digoxin and frusemide before operation, which was carried out when he was 8 days old, and after operation he was treated with phenobarbitone because of some twitching. He now attends a school for children with moderate learning difficulties. His blood pressure is 105/50 mm Hg and he has had no recurrence of the coarctation.

A girl of 5·9 years with aortic stenosis weighed 2380 g when she was born at 38 weeks' gestation. After operation at the age of 6 days she has progressed satisfactorily, growing with height and weight at the third centile, blood pressure 100/75 mm Hg and no recurrence of the coarctation.

A boy of 7·9 years with a ventricular septal defect, mitral stenosis, and aortic stenosis weighed 3010 g when born at full term. After operation at the age of 22 days he has grown at the 25th centile for height and weight, has had no recurrence of the coarctation, his blood pressure is 115/70 mm Hg, and on echocardiography there is normal left ventricular function, normal pulmonary artery pressure, trivial aortic incompetence, and an immobile posterior mitral leaflet.

A girl of 8·5 years with a ventricular septal defect, hypoplastic left ventricle, and hypoplastic mitral valve, weighed 4260 g when born at full term. She was in severe cardiac failure at presentation, was treated with digoxin and frusemide, and had several seizures after the operation, which was carried out when she was 9 days old. Her height is at the 90th centile, her weight at the 97th centile, her blood pressure is 90/60 mm Hg, and she has had no recurrence of the coarctation.

Discussion

Coarctation of the aorta is a common congenital cardiovascular malformation, and occurs more often among boys. In this series (from a supraregional cardiothoracic surgical centre) there was a male:female ratio of 1·5:1.

Newborn babies with critical aortic coarctation become symptomatic when the patent ductus arteriosus closes. Before this the femoral pulses may be easily palpable because of ductal blood flow. Ductal closure occurs at a variable time after birth, and our babies presented at ages starting at 1 day but the peak incidence occurred at about the age of 1 week. All the babies presented with cardiac failure.

The diagnosis of coarctation of the aorta should be considered in any baby in cardiac failure. Physical signs may include a systolic murmur, but the important finding is a difference in blood pressure (using an appropriately sized cuff) between the right upper limb and the lower limbs. This important sign will not be present in the rare case where there is an aberrant arterial supply to the right upper limb, if the supply originates beyond the coarctation when the right upper limb pressure is also low.

Babies in whom the diagnosis of coarctation of the aorta is suspected should be referred without delay to a cardiothoracic surgical centre with paediatric experience where definitive diagnosis can be made, generally by echocardiography, before urgent surgical correction.[6] Appropriate medical management should be instituted promptly while the transfer is being effected. After discussion with the staff at the referral unit, if the baby's condition is deteriorating or if there is likely to be substantial delay before transfer, an infusion of prostaglandin E_2 should be started. Our starting dose is 0·025 µg/kg/minute given by intravenous infusion. Larger doses are more likely to lead to episodes of apnoea or bradycardia. If the baby is in a poor haemodynamic state the merits and risks of adding dopamine to the infusion should be discussed with the staff at the referral unit.

The prognosis is determined primarily by the severity of any coexisting anomalies.[2] In our series there was no mortality if there were no associated anomalies. Of 15 babies with ventricular septal defects five died, all in the immediate postoperative period; three of these deaths, however, occurred in 1978 before we had started to use prostaglandin E_2 infusions. On the other hand, only four children have survived of the 14 who had more complicated associated anomalies.

Any complications, whether before, during, or after operation, influence mortality and morbidity. The introduction of intravenous prostaglandin infusions permitted more babies to have their operations without being in cardiac failure, or hypoxic, or acidaemic, or shocked, and is likely to have favourably influenced outcome.

There is debate about the best surgical technique,[7 8 10] and our experience may contribute to that debate. Whatever method of repair was used, we recommend continuing follow up of all patients, who may have recurrence of the coarctation (as occurred in 21% of our survivors) and who may develop systemic hypertension.[9]

We thank Dr N Wilson and Dr J Gibbs for helpful discussion and comment.

References

[1] Anyanwu E, Klemm C, Achatzy R, *et al*. Surgery of coarctation of the aorta: a nine year review of 253 patients. *Thorac Cardiovasc Surg* 1984;**32**:350–7.

[2] Hammon JW, Graham TP, Boucek RJ, Bender HW. Operative repair of coarctation of the aorta in infancy: results with and without ventricular septal defect. *Am J Cardiol* 1985;**55**:1555–9.

[3] Jammin P, Moulin D, Rubay J, *et al*. La coarctation de l'aorte chez le nourrisson. *Ann Chir* 1985;**39**:73–8.

[4] Nair UR, Jones O, Walker DR. Surgical management of severe coarctation of the aorta in the first month of life. *J Thorac Cardiovasc Surg* 1983;**86**:587–90.

[5] Waldhausen JA, Nahrwold DL. Repair of coarctation of the aorta with a subclavian flap. *J Thorac Cardiovasc Surg* 1966;**51**:532–3.

[6] Campbell DB, Waldhausen JA, Pierce WS, Fripp R, Whitman V. Should elective repair of coarctation of the aorta be done in infancy? *J Thorac Cardiovasc Surg* 1984;**88**:929–38.

[7] Cobanoglu A, Teply JF, Grunkemeier GL, Sunderland CO, Starr A. Coarctation of the aorta in patients younger than three months. *J Thorac Cardiovasc Surg* 1985;**89**:128–35.

[8] Korfer R, Meyer H, Kleikamp G, Bircks W. Early and late results after resection and end to end anastomosis of coarctation of the thoracic aorta in early infancy. *J Thorac Cardiovasc Surg* 1985;**89**:616–22.

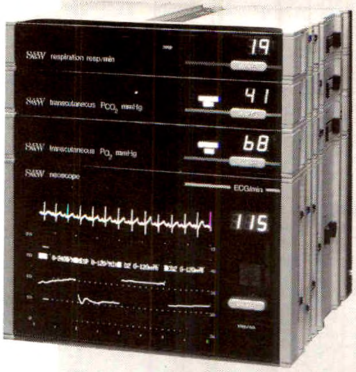
[9] Engle MA. A long look at surgery for coarctation of the aorta. *J Am Coll Cardiol* 1985;**6**:887–8.

[10] Regensburger D, Kyewalyanga N, Yankah AC. Chirurgische Behandlung der kritischen Aortenisthmusstenose im Sauglingsalter. *Klin Padiat* 1984;**196**:209–13.

Correspondence to Dr P Ehrhardt, St James's University Hospital, Beckett Street, Leeds LS9 7TF.

Accepted 14 November 1988

When Only The Best is Good Enough in Neonatal Care



The Neoscope has been designed specifically for neonatal use, with capabilities of displaying 3 dynamic wave forms, or 3 separate cardiorespirogram options. The modular design concept of the Neoscope system offers full flexibility at an affordable price, with modules available for all standard neonatal parameters.

The Diascope 2 is ideal where less sophisticated monitoring is required. All units include E.C.G. and temperature as standard, with options available for invasive pressure or respiration. The Diascope 2 can also be specified with an integral recorder. Used with optional integral batteries, it is particularly suitable when transferring neonates either externally between hospitals, or internally between departments.

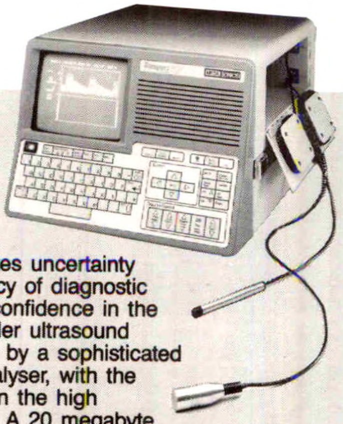
S&W manufacture and market a wide range of high quality technical products for use in the acute care areas of medicine.

For full details of all our products contact us at the address below.

S&W

Care for everybody.

S&W Vickers Ltd
Ruxley Corner
Sidcup
Kent DA14 5BL
Telephone: 01-309 0433
Telex: 896328
Fax: 01-309 0919



The Transcranial Doppler (T.C.D.) is a valuable diagnostic technique for Non Invasive assessment of Intracranial blood flow. The advanced technology eliminates uncertainty about the source and accuracy of diagnostic data thus greatly increasing confidence in the ultimate diagnosis. The Doppler ultrasound signal is computer processed by a sophisticated 256 point F.F.T. Spectrum Analyser, with the resulting analysis displayed on the high resolution flat screen monitor. A 20 megabyte hard disk allows storage of up to 400 Spectra.

n response to a growing demand or flexibility and convenience.

Combined package 1 (I+II)
Genotropin 12 IU
Recombinant somatropin
For i.m. and s.c. injection
The solution is prepared by adding 3 ml solvent
Gently dissolve the drug with a slow, swirling motion
The solution should not be shaken
Reconstituted Genotropin may be stored in the refrigerator for 2 weeks
Keep cold (+2°—+8°C)
Sterile powder
Genotropin 12
For i.m. and s.c. injec
Keep cold (+2°—+8°C)
KabiVitrum, Stockholm

Genotropin™ (somatropin (rbe)) is available in a 12 IU Multidose vial. Once reconstituted Genotropin 12 IU Multidose can be stored in a refrigerator for up to two weeks. This makes the use of individually titrated dosage regimens a practical proposition and reduces the time spent preparing injections.

The combination of authentic sequence growth hormone and multidose presentation makes the introduction of Genotropin 12 IU Multidose a significant development for patients requiring growth hormone therapy

Genotropin™ 12 IU Multidose

somatropin (rbe)

SCRIBING INFORMATION ▼ **Presentation** A vial of sterile lyophilised powder containing 12 IU somatropin (rbe) supplied with 3 ml of Water for Injections with 0.25% m-cresol for reconstitution. **Indications** The treatment
rt stature caused by decreased or absent secretion of pituitary growth hormone. **Reconstitution** Add 3 ml of Water for Injections with 0.25% m-cresol to the lyophilised powder in the vial. Dissolve the drug gently without shak
rously. **Dosage and Administration** Administer by subcutaneous or intramuscular injection. Generally a dose of 0.5 - 0.7 IU/kg body weight per week is recommended divided into six or seven subcutaneous injections. Alternativ
to three intramuscular injections can be given. **Contra-Indications** Only patients with unfused epiphyses should be treated. **Precautions** Patients with diabetes mellitus may require adjustment of their antidiabetic therapy. Patie
ted with Genotropin should be regularly assessed by a child growth specialist. If given subcutaneously, the injection site should be rotated to prevent lipoatrophy. **Pregnancy and Lactation** In the event of pregnancy occurring dur
otropin therapy, treatment should be discontinued. No information is available as to whether peptide hormones pass into breast milk. **Side-Effects** A few children developed transient local skin reactions during clinical trials. So
ents develop antibodies to growth hormone although the frequency with Genotropin has been low in clinical trials. **Pharmaceutical Precautions** Store between 2-8 C and protect from light. Reconstituted Genotropin 12 IU Multid
y be stored for up to 2 weeks in the refrigerator. **Legal Category** POM. **Package Quantities** Combined pack containing one vial of somatropin (rbe) 12 IU and one vial of Water for Injections with 0.25% m-cresol. **Product Lice**
mbers Genotropin 12 IU Multidose PL 0022/0079. Water for Injections with 0.25% m-cresol PL 0022/0081. **Price** NHS Price £91.50. **Product Licence Holder** KabiVitrum Ltd. KabiVitrum House. Riverside Way. Uxbridge. Middlesex UB8 2
ther information is available on request from the product licence holder.

Archives of Disease in Childhood, 1989, **64,** 333–337

Factors associated with developmental progress of full term neonates who required intensive care

L LUDMAN, R LANSDOWN, AND L SPITZ

Institute of Child Health, Hospital for Sick Children, Great Ormond Street, London

SUMMARY The development of 43 infants born at full term, who were admitted to neonatal intensive care units shortly after birth, was compared in a prospective longitudinal study with that of a group of 29 healthy newborn babies. Thirty infants required emergency operations during the neonatal period, and 13 were admitted for medical reasons. The effects of being in hospital and being separated from their mothers were also studied. At 1 year the 'sick' babies were performing significantly less well in almost all areas of development. In the group of sick infants, the mothers' mental health explained 25% of the variance in developmental outcome at 6 months. At 1 year the most important predictor was length of stay in hospital, which explained 35% of the variance.

The developmental outcome of infants who were premature, small for gestational age, of low birth weight, and more recently of very low birth weight (VLBW) has been the focus of extensive psychological research,[1-8] and it is well established that preterm babies have more mental and behavioural problems in childhood than infants born at full term.[8] An important group of sick newborn babies are those born at full term who require intensive care for conditions that may necessitate either emergency operations or intensive medical treatment. These babies and their families experience many of the problems associated with prematurity, but we know of no previous study of their developmental outcome. A three year prospective longitudinal study is being carried out to examine the intellectual, social, and emotional development of two groups of sick infants born at full term. The main group comprises 30 infants admitted for emergency operations within the neonatal period, and a smaller group of 13 infants who required intensive medical care at birth. In this paper we report their developmental progress up to the age of 1 year.

Patients and methods

The study group of sick infants comprised 43 newborn infants born at full term. Thirty were admitted to the neonatal surgical unit at the Hospital for Sick Children, Great Ormond Street, during the period November 1983 to December 1984, and 13 were admitted for neonatal intensive care either to the same hospital or to Queen Charlotte's Maternity Hospital (table 1). Twenty nine healthy newborn infants were matched with the surgical group for sex, social group, mother's age and marital status, birth order, and geographical location, and these constitute the control group. This group was collected during the period December 1983 to October 1985. There were no significant differences between the groups for sex, social group, birth order, or mother's age or marital status (table 2).

A standardised assessment of the severity of each infant's condition was made using the Parmelee postnatal complication scale,[9] which assesses the infant's postnatal course within the first month of life, and includes conditions that reflect an increased risk of mortality and morbidity such as ventilation and metabolic disturbance. The possible range of scores is from 55 to 160 with higher scores having a better prognosis. The median score for the sick babies was 77 (range 55–87).

The birth weights of 41 of the sick babies were between 2000–4500 g. One baby with hydrops weighed more than 4500 g, and one who was small for gestational age weighed 1980 g. Gestational age was equal to or greater than 37 weeks. Fourteen (33%) required ventilation, and of these 10 (23%)

Table 1 *Diagnoses in 43 children born at full term who required neonatal intensive care*

Diagnosis	*Total No of children*	*No with multiple abnormalities*
Surgical patients:		
Oesophageal atresia and tracheo-oesophageal fistula	5	4
Diaphragmatic hernia	4	0
Anorectal abnormalities	4	1
Necrotising enterocolitis	4	1
Gastroschisis	2	0
Meconium ileus	2	1
Antral atresia	1	0
Duodenal atresia	1	1
Malrotation	1	0
Ileal stenosis	1	0
Hirschsprung's disease	1	0
Nasal obstruction	1	0
Wilms's tumour	1	0
Sacrococcygeal teratoma	1	0
Lumbar meningomyelocele	1	0
Medical patients:		
Pneumonia	3	0
Necrotising enterocilitis	2	0
Respiratory distress	2	0
Congenital infection	1	0
Meningitis	1	0
Hydrops	1	0
Birth asphyxia	1	0
Pneumonitis and pulmonary hypertension	1	0
Aspiration syndrome	1	0

were ventilated for more than four days. The median duration of the first admission (including time spent in local hospitals) was 22 days (range 7–91). Seventeen were readmitted for varying lengths of time before the age of 6 months, and a further nine before the age of 1 year. The median length of stay in hospital by the age of 1 year was 28 days (range 7–365).

The families were studied intensively during the first year. The initial interview with the parent(s) took place in the hospital. All subsequent interviews and assessments (at 6 weeks, 6 months, and 1 year) were conducted in the family home. At each stage the mother was interviewed using a semistructured interview. This covered many aspects of family life and relationships, including the marital relationship,[10] support, and stress factors. The mothers' mental health was assessed using Goldberg's standardised psychiatric interview[11] and general health questionnaire.[12] At 6 months and 1 year the Griffiths's mental development scales[13] were used to assess the infants' development. The interviews and assessments were performed by the research psychologist (LL) conducting the study.

Table 2 *Demographic details of the two groups*

	No (%) of study group (n=43)	*No (%) of control group (n=29)*
Sex:		
Male	19 (44)	8 (28)
Female	23 (56)	21 (72)
Social group:		
Father non-manual worker	21 (49)	13 (45)
Father manual worker	15 (35)	12 (41)
Single mother	7 (16)	4 (14)
Marital status of mother:		
Married	36 (84)	25 (86)
Single	7 (16)	4 (14)
Mother's age:		
<25	14 (33)	14 (48)
25 or more	29 (67)	15 (52)
Parity:		
Primiparous	23 (53)	15 (52)
Multiparous	20 (47)	14 (48)

The Statistical Package for the Social Sciences (SPSS–X) multiple regression techniques were used to examine the association between possible predictors and developmental outcome. Where distributional characteristics dictated (for example, the distribution of length of stay in hospital) appropriate logarithmic transformations were made. The significance of differences between means was assessed by Student's t test or one way analysis of variance, as appropriate, a p value of <0.05 being accepted as significant.

Results

DEVELOPMENTAL OUTCOME (GRIFFITHS'S SCALE)

There were no significant differences between the groups at 6 months. At 1 year there were significant differences in five of the seven Griffiths's scales (table 3). The mean general developmental quotient and mental age (weeks) of the sick infants were significantly lower than those of the control infants. In addition the sick infants scored significantly less well in hearing and speech, and had poorer fine motor control. Their locomotor development was also significantly slower.

MENTAL HEALTH OF MOTHERS

The degree of psychiatric morbidity as assessed by the general health questionnaire at 6 weeks, and by the standardised psychiatric interview at 1 year, was significantly greater among mothers of the sick infants than among the mothers of the control infants ($p=0{\cdot}04$ and $p=0{\cdot}02$, respectively, Mann-Whitney U test).

Table 3 *Developmental quotients in the two groups at the age of 1 year*

Griffiths's scales	*Mean (SD) score in study group (n=41)**	*Mean (SD) score in control group (n=27)†*	*p Value*
General quotient	102·92 (15·23)	109·11 (7·52)	0·03
Mental age (weeks)	54·99 (8·14)	58·35 (4·39)	0·03
Motor	108·19 (24·76)	118·00 (13·97)	0·04
Personal/social	101·21 (14·77)	102·29 (5·96)	0·67
Hearing/speech	94·43 (16·90)	100·62 (7·14)	0·04
Eye/hand	105·53 (13·64)	113·74 (9·69)	0·005
Performance	105·39 (17·03)	111·11 (14·95)	0·16

*One baby was severely subnormal and excluded from developmental testing and one baby was adopted. †Two families declined to continue.

The factors having the most influence on the development of the sick infants at 6 months were the mental state of the mother ($\beta=-0{\cdot}498$), length of stay in hospital ($\beta=-0{\cdot}414$), repeated stays in hospital ($\beta=-0{\cdot}344$), and postnatal complication scale scores ($\beta=0{\cdot}332$). Because the last three variables were strongly intercorrelated, length of stay in hospital (the variable most strongly associated with developmental outcome), was used as the main predictor in multivariate regression analyses. SPSS-X stepwise regression showed that 25% of the variability in the general quotient was explained by the mothers' mental health scores (F(1,41) 13.49, $p<0{\cdot}001$). When length of stay in hospital was forced into a standard regression analysis first, it explained 17% of the variance (F(1,41) 8.49, $p=0{\cdot}006$). These two variables in combination contributed 31% of the variability (F(2,40) 8.84, $p<0{\cdot}001$).

At 1 year stepwise regression analysis showed that length of stay in hospital was the single predictor that explained 35% of the variance (F(1,39)21.25, $p<0{\cdot}0001$). Univariate analyses indicated that postnatal complication scale scores ($\beta=0{\cdot}374$, p.02) and social group I (non-manual occupations) ($\beta=0{\cdot}339$, p.03) were also significant variables. Because postnatal complication scale scores were correlated with length of stay in hospital ($r=-0{\cdot}579$) they were again dropped from the multivariate analyses. The coefficient for the social group variable when social group I was coded as 1, indicated that the babies with fathers in non-manual occupations have general quotients that are estimated to be about 4% greater than other social groups after statistical adjustment for length of stay in hospital.

Discussion

At 6 months the developmental progress of the sick babies was comparable with that of the control infants, but at 1 year they were performing significantly less well in almost all areas of development. Developmental quotients were generally within the normal range, but one infant was mentally handicapped and three infants had general quotients that were more than two standard deviations below the mean. The general quotients of all the infants in the control group were within the normal range.

The psychological state of the mother was the best predictor of the sick infants' development at 6 months. Infants with mothers who were experiencing psychological difficulties were more likely to have lower general quotient scores (table 4). The length of stay in hospital (table 5) also seemed to be an important factor and, together with standardised psychiatric interview scores, explained 31% of the variability in general quotient scores. By the time the babies were 1 year old the most important predictor of the sick infants' developmental progress was the total length of stay in hospital (35% of the variance). Another important factor was the severity of the infants' condition in the neonatal period. This was strongly correlated with the length of time an infant spent in hospital, indicating a strong association between these two variables during the first year of life. Parental social group became a relatively important factor at 1 year, babies with parents in non-manual occupations being more likely to have higher general quotient scores.

The association between the mothers' psychiatric disturbances and the sick infants' developmental progress indicates that a depressed mother may interact less with her sick infant in the early months. Furthermore it is probable that the sick infants were not as responsive to their parents as normal infants. Interestingly, the developmental progress of infants in the control group was not adversely affected if the mothers had psychological problems. There were no differences between the groups on the ratings of the quality of the marriage, but there was a strong

Table 4 *Developmental quotients at 6 months by mothers' mental health as measured by Goldberg's standardised psychiatric interview*

Griffiths's scales Mean (SD)	*Mothers' mental health score groups*		*p Value*
	Low score (<14) *(n=33)*	*High score (≥14)** *(n=10)*	
General quotient	101·48 (7·46)	87·70 (26·62)	<0·01
Mental age (weeks)	27·91 (3·2)	24·10 (9·56)	0·05
Motor	103·30 (12·02)	87·40 (31·63)	0·02
Personal/social	106·88 (8·79)	91·50 (29·08)	<0·01
Hearing/speech	89·61 (8·80)	77·10 (20·96)	0·009
Eye/hand	102·55 (9·30)	87·30 (37·06)	0·03
Performance	105·21 (12·57)	92·60 (27·73)	0·05

*Indicative of probable psychiatric illness.

Table 5 *Developmental quotients at 1 year by length of stay in hospital (n=41)*

Griffiths's scales Mean (SD)	*Length of stay in hospital*		*p Value*
	<28 days *(n=22)*	*≥28 days* *(n=19)*	
General quotient	108·64 (10·66)	96·32 (17·23)	0·008
Mental age (weeks)	58·05 (5·43)	51·46 (9·41)	0·008
Motor	116·45 (17·93)	98·63 (28·43)	0·02
Personal/social	105·09 (7·70)	96·74 (19·40)	0·07
Hearing/speech	100·23 (10·61)	87·74 (20·37)	0·02
Eye/hand	111·14 (10·63)	99·05 (14·10)	0·003
Performance	110·73 (17·42)	99·21 (14·68)	0·03

association between maternal depression and poor marriages. This confirms the findings of other studies.[14,15]

The parents of the sick babies were under greater general stress than those of the control group. A stress score was calculated for each family by adding the serious stress factors affecting it. These included stress caused by bereavement, financial difficulties, housing, and problems at work. Stress scores in the 12 months before the birth of the index child were similar for the two groups, but at each subsequent stage of the study the scores were significantly higher in the families with sick babies. These findings suggest that it is a combination of factors rather than just the anxiety associated with the birth of a sick baby that contributes to the increased incidence of maternal depression. Mothers of sick babies may therefore benefit from guidance and support in the months after discharge, which should help to alleviate some of the difficulties experienced by the families and, in so doing, improve their psychological state. This is important, because their babies seem to be more vulnerable to the effects of depression on the mother/infant interactions than do the healthy controls. Moreover, a recent study has shown that maternal depression during the first year of life may have longer term consequences for cognitive development.[16] An important finding of the present study was that maternal depression was not associated with postpartum separation, nor to the length of the separation caused by the infants' stay in hospital. In addition, length of stay in hospital was not associated with problems in the parental relationship.

Despite the separation of mother and infant and the increased incidence of depression and anxiety in the mothers of the sick infants, the mother/child relationships were generally as loving and secure as those in the control group. Data about the mother/infant relationships will be reported elsewhere.

In conclusion, our findings indicate that sick babies born at full term are, as a group, developmentally slower at 1 year than a group of healthy babies. The follow up study at 3 years will show whether this effect persists.

This research was supported by grants from the Nuffield Foundation, the University of London, and the Lowe-Costello fund. We thank Mr EM Kiely, Mr RJ Brereton, Dr R Dinwiddie, and Dr D Harvey for allowing us to include their patients in the study, and Mrs A Dawkins (Institute of Education) and Dr M Smith (Institute of Child Health) for statistical advice. We also thank the parents of the infants for participating in the study.

References

[1] Marlow N, D'Souza SW, Chiswick ML. Neurodevelopmental outcome in babies weighing less than 2001 g at birth. *Br Med J* 1987;**294**:1582–6.

[2] Hunt JV. Predicting intellectual disorders in childhood for preterm infants with birthweights below 1501 gm. In: Friedman SL, Sigman M, eds. *Preterm birth and psychological development.* New York: Academic Press, 1981.

[3] Ferrari F, Grosoli MV, Fontana G, Cavazzuti GB. Neurobehavioural comparison of low-risk preterm and full term infants at term conceptional age. *Dev Med Child Neurol* 1983;**25**:450–8.

[4] Fancourt R, Campbell S, Harvey D, Norman AP. Follow-up study of small for dates babies. *Br Med J* 1976;**i**:1436–7.

[5] Siegal LS. Reproductive, perinatal, and environmental factors as predictors of the cognitive and language development of preterm and full-term infants. *Child Dev* 1982;**53**:963–73.

[6] Sigman M, Parmelee AH. Longitudinal evaluation of the preterm infant. In: Field T, ed. *Infants born at risk.* New York: Spectrum Publications, 1979.

[7] Cohen SE, Sigman M, Parmelee AH, Beckwith L. Perinatal risk and developmental outcome in preterm infants. *Semin Perinatol* 1982;**5**:334–97.

[8] Davies PA, Stewart A. Low-birth weight infants: neurological sequelae and later intelligence. *Br Med Bull* 1975;**31**:85–91.

[9] Littman B, Parmelee AH. Medical correlates of infant development *Pediatrics* 1978;**61**:470–4.

[10] Quinton DA, Rutter M, Rowlands O. An evaluation of an interview assessment of marriage. *Psychol Med* 1976;**6**:577–86.

[11] Goldberg D, Eastwood MR, Kedward HB, *et al.* A standardized psychiatric interview for use in community surveys. *British Journal of Preventive and Social Medicine* 1970;**24**:18–23.

[12] Goldberg DF. *Manual of the general health questionnaire.* Windsor: National Foundation for Educational Research, 1978.

[13] Griffiths R. *The abilities of young children.* London: Child Development Research Centre, 1970.

[14] Watson JP, Elliott AJ, Rugg AJ, Brough DI. Psychiatry disorder in pregnancy and the first postnatal year. *Br J Psychiatry* 1984;**144**:453–62.

[15] Cox JL, Connor Y, Kendell RE. Prospective study of the psychiatric disorders of childbirth. *Br J Psychiatry* 1982;**140**: 111–7.

[16] Cogill SR, Caplan HL, Alexandra H, Robson KM, Kumar R. Impact of maternal postnatal depression on cognitive development of young children. *Br Med J* 1986;**292**:1165–7.

Correspondence to Mrs Lorraine Ludman, Department of Child Psychiatry, Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

Accepted 26 October 1988

Archives of Disease in Childhood, 1989, **64**, 338–342

Value of selective screening for congenital adrenal hyperplasia in Hungary

J SÓLYOM* AND I A HUGHES†

**Second Department of Paediatrics, Semmelweis University Medical School, Budapest, and †Department of Child Health, University of Wales College of Medicine, Cardiff*

SUMMARY Measurement of the 17-hydroxyprogesterone concentration in blood spots was used to identify cases of congenital adrenal hyperplasia among patients with inappropriate virilisation, or salt wasting, or both. Between 1978 and 1986 61 were identified among 707 patients (278 neonates, 204 infants, and 225 children).

The incidence of classic congenital adrenal hyperplasia was calculated for a seven year prospective trial period using the blood spot 17-hydroxyprogesterone method in selective screening. There were 38 salt losers and 14 simple virilisers in 968 303 live births, an incidence of congenital adrenal hyperplasia of 1:18 000 in the Hungarian population. Selective screening led to earlier diagnosis of congenital adrenal hyperplasia and a pronounced decrease in mortality. A central laboratory to measure the blood spot 17-hydroxyprogesterone concentrations is valuable for the investigation of patients at risk for congenital adrenal hyperplasia in countries where blood steroid assays are not readily available.

Congenital adrenal hyperplasia is the result of 21-hydroxylase enzyme deficiency in more than 90% of cases.[1] The plasma 17-hydroxyprogesterone concentration is usually raised and its measurement is a rapid and reliable test in patients suspected of having congenital adrenal hyperplasia.[2–4] Though the assay is routinely available in steroid laboratories in western countries, in other countries such as Hungary the techniques for the provision of rapid results are seldom available.

A method for the measurement of 17-hydroxyprogesterone in blood spotted on to filter paper was first reported in 1977.[5] The method was originally intended for the screening of neonates for congenital adrenal hyperplasia, but a modified blood spot method was developed for the rapid diagnosis of patients suspected of having congenital adrenal hyperplasia throughout Hungary.[6] Preliminary experience with the use of a blood spot 17-hydroxyprogesterone assay to detect infants at risk of congenital adrenal hyperplasia has been previously reported.[7] This paper reports on the use of this test to screen more than 700 patients at risk during an eight year period. The results also provide information on the incidence of congenital adrenal hyperplasia in Hungary.

Patients and methods

Between October 1978 and December 1986, 707 patients considered to be at risk of developing congenital adrenal hyperplasia were studied. The indications for investigation were inappropriate virilisation at any age, or salt wasting during the first month of life. The number of patients investigated in each age group was as follows: 1–3 days, 67; 4–7 days, 73; 8–30 days, 138; 2–3 months, 145; 4–12 months, 59; 2–8 years, 145; 9–18 years, 80.

Capillary blood was spotted on to the filter paper cards that are routinely used for the screening of neonates for phenylketonuria and congenital hypothyroidism. Samples were collected during the morning from patients older than 2 months of age because of the decline in 17-hydroxyprogesterone concentrations that occurs later in the day.[8] Cards were posted to a central laboratory; the stability of steroids in dried blood spots kept at room temperature for 150 days has been reported previously.[9] Serial capillary blood samples were also collected from some patients with congenital adrenal hyperplasia before treatment was started.

The assay for the measurement of blood spot 17-hydroxyprogesterone concentration has been published in detail.[6] [10] The sensitivity of the method was 10 pg/disc, equivalent to 10 nmol/l of serum. Results were available within 24 hours of receiving the sample in the laboratory.

Results

During the eight year study period 61 patients with 21-hydroxylase deficiency were identified using the blood spot 17-hydroxyprogesterone method among 707 patients with suspected congenital adrenal hyperplasia. The distribution of blood spot 17-hydroxyprogesterone values in each age group is shown in figs 1, 2, and 3.

Twenty six infants with salt losing congenital adrenal hyperplasia were identified among 278 patients investigated at age 1–30 days because of ambiguous genitalia, or salt wasting, or both (fig 1). The values of 17-hydroxyprogesterone at age 4–7 days were higher in ill babies born at full term and healthy premature infants compared with healthy babies born at full term (range: 10–140 nmol/l). Using a cut off value of 17-hydroxyprogesterone of 240 nmol/l for the diagnosis of congenital adrenal hyperplasia there were five false positive and no false negative cases. Three of these infants were boys with hyponatraemia secondary to renal tract malformations and infection. The other two infants were premature girls in whom the clitoris was prominent.

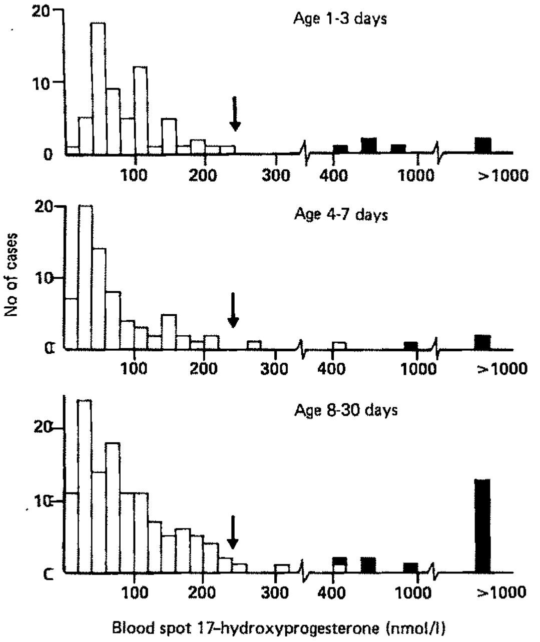


Fig 1 *Frequency distribution of blood spot 17-hydroxyprogesterone values in infants at risk of congenital adrenal hyperplasia during the first month of life. Closed bars represent infants with congenital adrenal hyperplasia; there were six of 67 at age 1–3 days, three of 73 at age 4–7 days, and 17 of 138 at age 8–30 days. The arrow denotes the selected cut off value for 17-hydroxyprogesterone.*

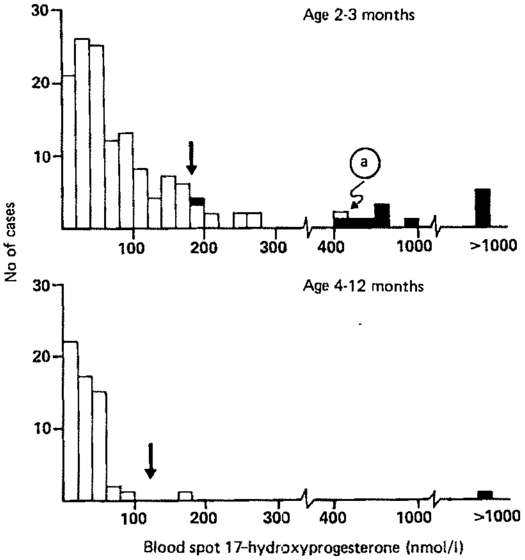


Fig 2 *Frequency distribution of blood spot 17-hydroxyprogesterone values in children aged 2–12 months at risk of congenital adrenal hyperplasia; (a) indicates an infant with 11β-hydroxylase deficiency. Closed bars represent infants with congenital adrenal hyperplasia; there were 13 of 145 at age 2–3 months and one of 59 at age 4–12 months. The arrow denotes the selected cut off value for 17-hydroxyprogesterone.*

Fig 4 shows the results of serial blood spot 17-hydroxyprogesterone meaurements in infants with congenital adrenal hyperplasia compared with those from healthy babies born at full term, and very low birthweight premature infants without congenital adrenal hyperplasia. There was some overlap in 17-hydroxyprogesterone values on the first day of life, when three very low birthweight premature infants had concentrations above 500 nmol/l. Their raised values declined rapidly over a few days, however, whereas blood spot 17-hydroxyprogesterone concentrations in infants with congenital adrenal hyperplasia showed pronounced increases.

Fourteen patients with 21-hydroxylase deficiency (two of whom were not salt losers) were identified from 204 infants aged 2–12 months who were investigated for problems such as failure to thrive, dehydration, and enlarged clitoris with labial fusion.

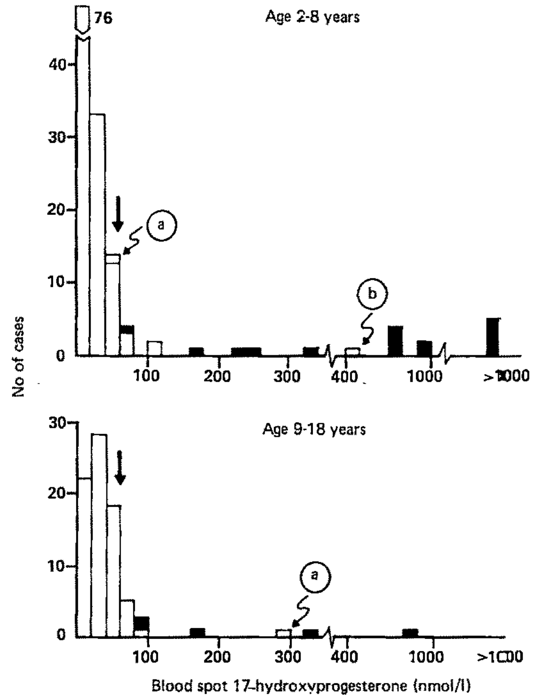


Fig 3 *Frequency distribution of blood spot 17-hydroxyprogesterone values in children at risk of congenital adrenal hyperplasia at 2–18 years; (a) and (b) indicate patients with 11β-hydroxylase deficiency and virilising adrenal carcinoma, respectively. Closed bars represent infants with congenital adrenal hyperplasia; there were 16 of 145 at age 2–8 years and five of 80 at age 9–18 years. The arrow denotes selected cut off value for 17-hydroxyprogesterone.*

(fig 2). Blood spot 17-hydroxyprogesterone cut off limits of 180 and 120 nmol/l at 2–3 and 4–12 months, respectively, identified all the patients with congenital adrenal hyperplasia. Of 11 false positive results, one infant had 11β-hydroxylase deficiency; the other 10 patients had normal blood spot 17-hydroxyprogesterone concentrations when the test was repeated. Among 225 patients aged 2–18 years who had either premature pubarche or hirsutism there were 21 cases of congenital adrenal hyperplasia (including 14 who were not salt losers, and seven who had the late onset form) who were identified using a cut off value of 17-hydroxyprogesterone of 60 nmol/l. Different cut off points for 17-hydroxyprogesterone in each age group were needed to avoid false negative results and ensure as low a number as possible of false positive results. Among the false positive results were a patient with an adrenal carcinoma and two cases of 11β-hydroxylase deficiency. The median time from birth to the diagnosis of congenital adrenal hyperplasia in 38 salt losing cases was 17 days (range four to 38). This compares with 35 days (range 7–120) in a comparable number of salt losing cases analysed in a retrospective study.

Table 1 shows the number of patients with congenital adrenal hyperplasia born in Hungary during a 20 year period from 1966 to 1985. The cases were found by examination of hospital medical records and later (from 1979 to 1985) prospectively

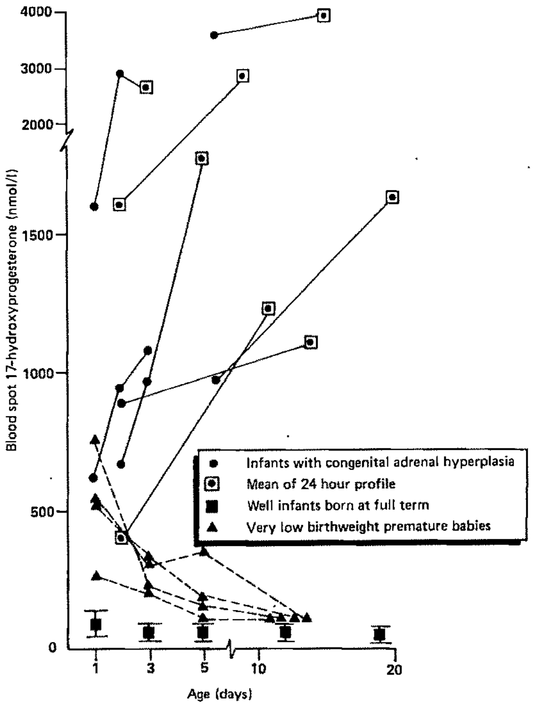


Fig 4 *Serial blood spot 17-hydroxyprogesterone values in eight infants with congenital adrenal hyperplasia and in 12 infants born at full term and four very low birthweight infants without congenital adrenal hyperplasia during the first 20 days of life. Figures are given as mean (SD).*

Table 1 *Number of patients with congenital adrenal hyperplasia born in Hungary, 1966–1985*

Enzyme defect	*Girls*	*Boys*	*Total No*
21-hydroxylase:			
Salt losers	37	42	79
Simple virilisers	25	18	43
Late onset	11	2	13
11β-hydroxylase	1	3	4

Table 2 *Incidence of classic congenital adrenal hyperplasia in Hungary*

Method of analysis	*Period of survey*	*No of live births*	*No of cases*			*Estimated incidence*
			Salt losers	*Simple virilisers*	*Total No*	
Retrospective case survey	1966–1978	2 119 727	41	29	70	1:30 282
Prospective selective screening	1979–1985	968 303	38	14	52	1:18 621

by measurement of blood spot 17-hydroxyprogesterone values in patients at risk. There was an equal incidence in boys and girls and two thirds were salt losers. The incidence of congenital adrenal hyperplasia among live births during the 20 year period was 1:25 312. The incidence for the last seven years of this period is shown in table 2. The estimated incidence was higher during the period of selective screening compared with that obtained by retrospective analysis. The presumed incidence of congenital adrenal hyperplasia in Hungary between 1979 and 1985 was 1:18 600 with 95% confidence limits of 1:14 642 to 1:25 572. One country area had 11 salt losers during this period (1966–1985), an incidence five times greater than that in the whole country.

Discussion

This study shows the value of 17-hydroxyprogesterone measurements in identifying congenital adrenal hyperplasia among patients within a wide age range with inappropriate virilisation or salt wasting. The restriction of screening to a population at risk rather than mass screening at birth is an option recently introduced in Italy.[11] The present study reports the largest series of infants with congenital adrenal hyperplasia identified during the neonatal period by the blood spot 17-hydroxyprogesterone method. The results confirm previous reports of the accuracy of this method for screening for congenital adrenal hyperplasia in the newborn.[12–14] We found a higher false positive rate because those patients at risk were more likely to have, for example, salt wasting than the population identified by mass screening. Acute illness in infants, particularly if they are premature, can lead to the secretion of large amounts of adrenocortical hormones.[15–16] Steroid concentrations normally fall rapidly once the stressful period is over. Diagnosis when there are only moderate rises of 17-hydroxyprogesterone concentrations above the cut off value for age, as in 11β-hydroxylase deficiency, requires detailed plasma steroid analysis and specific gas chromatographic determination of urinary steroid excretion.

In a recent workshop on screening for congenital adrenal hyperplasia[17] it was emphasised that the increased awareness of cases at risk (listed in table 3) and the ready availability of a rapid 17-hydroxyprogesterone assay[4] should result in a low incidence of undetected classical cases of congenital adrenal hyperplasia. A retrospective survey of 117 patients with congenital adrenal hyperplasia in Birmingham during a 30 year period showed an improvement in early diagnosis in children born after 1970.[18] The change was attributed to the factors previously mentioned, and the authors concluded that a neonatal screening programme for congenital adrenal hyperplasia in the UK was not necessary. The need is clearly different in Hungary where routine 17-hydroxyprogesterone measurements are not yet available. A central laboratory that is able to provide rapid results of 17-hydroxyprogesterone concentrations in blood spots collected from a restricted group at risk is a satisfactory alternative. The procedure has led to earlier diagnosis and treatment, and a reduction in mortality from 27% in 1966–78 to 8% in 1979–85.

Data are now available from a national register of all cases of congenital adrenal hyperplasia in Hungary. The ratio of salt losers to simple virilisers in classic congenital adrenal hyperplasia and the incidence of 1:18 000 are similar to those in other European countries.[19–21] One region of Hungary seems to have an increased incidence of salt losing congenital adrenal hyperplasia, although it is still lower than those reported from Alaska[22] and La Reunion.[14] Selective screening for congenital adrenal hyperplasia is a practical option that can yield valuable clinical information and more accurate estimate of incidence.

Table 3 *Cases of congenital adrenal hyperplasia readily identifiable at birth*

- All affected girls (theoretically)
- Salt losers
- Apparent cryptorchid boys with hypospadias
- Those with a previous family history of congenital adrenal hyperplasia
- Those with a positive prenatal diagnosis

References

[1] Hughes IA. Congenital and acquired disorders of the adrenal cortex. *Clin Endocrinol Metab* 1982;**11**:89–125.

[2] Youssefnejadian E, David R. Early diagnosis of congenital adrenal hyperplasia by measurement of 17-hydroxyprogesterone. *Clin Endocrinol* 1975;**4**:451–4.

[3] Hughes IA, Fahmy DR, Griffiths K. Plasma 17OH-progesterone concentrations in newborn infants. *Arch Dis Child* 1979;**54**: 347–9.

[4] Dyas J, Read GF, Guha-Maulik T, Hughes IA, Fahmy DR. A rapid assay for 17OH-progesterone in plasma, saliva and amniotic fluid using a magnetisable solid-phase antiserum. *Ann Clin Biochem* 1984;**21**:421–4.

[5] Pang S, Hotchkiss J, Drash AL, Levine LS, New MI. Microfilter paper method for 17-hydroxyprogesterone radioimmunoassay: its application for rapid screening for congenital adrenal hyperplasia. *J Clin Endocrinol Metab* 1977;**45**:1003–8.

[6] Sólyom J, Hammond GL, Vihko R. A method for identification and follow-up of patients with a steroid 21-hydroxylase deficiency. *Clin Chim Acta* 1979;**92**:117–24.

[7] Sólyom J, Hervei S, Marossy P, Sólyom E, Babosa M, Szombathy G. "Dot-17alpha-hydroxyprogesterone" radioimmunoassay for identification of congenital adrenal hyperplasia in young infants. *Acta Paediatr Scand* 1981;**70**:913–7.

[8] Sólyom J. Diurnal variation in blood 17-hydroxyprogesterone concentrations in untreated congenital adrenal hyperplasia. *Arch Dis Child* 1984;**59**:743–7.

[9] Sólyom J. Analysis of steroid hormones in biological samples dried on filter paper. In: Görög S. *Advances in steroid analysis.* Budapest: Akadémiai Kiadó, 1982:201–5.

[10] Sólyom J. Comparative measurements of serum concentration and blood spot level of 17-hydroxyprogesterone in congenital adrenal hyperplasia. In: Görög S. *Advances in steroid analysis.* Budapest: Akadémiai Kiadó, 1985:207–11.

[11] Cacciari E, Balsamo A, Cassio A, *et al.* Neonatal screening programme for congenital adrenal hyperplasia in a homogeneous Caucasian population. *J Inherited Metab Dis* 1986;**9**(suppl 1):142–6.

[12] Shimozawa K, Saisho S, Saito N, *et al.* A neonatal mass-screening for congenital adrenal hyperplasia in Japan. *Acta Endocrinol* 1984;**107**:513–8.

[13] Wallace AM, Beastall GH, Cook B, *et al.* Neonatal screening for congenital adrenal hyperplasia: a programme based on a novel direct radioimmunoassay for 17-hydroxyprogesterone in blood spots. *J Endocrinol* 1986;**108**:299–308.

[14] Dhondt JL, Dorche C, Farriaux JP, Courte C. Neonatal screening for congenital adrenal hyperplasia: a pilot study in France. *J Inherited Metab Dis* 1986;**9**(suppl 1):147–51.

[15] Murphy JF, Joyce B, Dyas J, Hughes IA. Plasma 17-hydroxyprogesterone concentrations in ill newborn infants. *Arch Dis Child* 1983;**58**:532–4.

[16] Hughes D, Murphy JF, Dyas J, Robinson JA, Fahmy DR, Hughes IA. Blood spot glucocorticoid concentrations in ill preterm infants. *Arch Dis Child* 1987;**62**:1014–8.

[17] Hughes IA. Clinical aspects of congenital adrenal hyperplasia: early diagnosis and prognosis. *J Inherited Metab Dis* 1986;**9**(suppl 1):115–23.

[18] Virdi NK, Rayner PHW, Rudd BT, Green A. Should we screen for congenital adrenal hyperplasia? A review of 117 cases. *Arch Dis Child* 1987;**62**:659–62.

[19] Werder EA, Siebenmann RE, Knorr-Murset G, *et al.* The incidence of congenital adrenal hyperplasia in Switzerland: a survey of patients born in 1960–1974. *Helv Paediatr Acta* 1980;**35**:5–11.

[20] Murtaza L, Sibert JR, Hughes IA, Balfour IC. Congenital adrenal hyperplasia—a clinical and genetic survey. *Arch Dis Child* 1980;**55**:622–5.

[21] Bois E, Mornet E, Chompret A, *et al.* L'hyperplasie congenitale des surrénales (21-OH) en France. Génétique des populations. *Arch Fr Pediatr* 1985;**42**:175–9.

[22] Pang S, Murphy W, Levine LS, *et al.* A pilot newborn screening for congenital adrenal hyperplasia in Alaska. *J Clin Endocrinol Metab* 1982;**55**:413–20.

Correspondence and requests for reprints to Dr J Sólyom, 2nd Department of Paediatrics, Semmelweis University Medical School, H-1094 Budapest, Tuzoltó u.7, Hungary.

Accepted 18 July 1988

Archives of Disease in Childhood, 1989, **64,** 343–345

Changes in trimethoprim pharmacokinetics after the newborn period

K HOPPU

Children's Hospital and Department of Clinical Pharmacology, University of Helsinki, Helsinki, Finland

SUMMARY The pharmacokinetics of trimethoprim administered orally or intravenously were investigated in six infants aged 1·7 months to 1·1 years. In these infants trimethoprim had a mean half life of 4·6 hours; this was comparable with the values found in young and school age children (3·8 and 5·4 hours respectively) and about a quarter of the half life in newborns. The volume of distribution (1·5 l/kg) was smaller than in newborns but larger than in young or school age children (0·9 and 1·1 l/kg respectively). The plasma clearance in these infants (3·3 ml/min/kg) was slightly larger than in newborns or in either group of older children (2·9 and 2·4 ml/min/kg respectively). Thus the most dramatic changes in trimethoprim pharmacokinetics seem to occur during the first two months of life. A reduced daily dose of trimethoprim is necessary during the first two months only. An increased daily dose, by addition of a third dose each day, is recommended from two months.

Trimethoprim, mostly in combination with a sulphonamide, may be used in infants to treat severe infections.[1] The age related changes in trimethoprim pharmacokinetics indicate that, as compared with adults, newborn babies need smaller[2] and children larger doses.[3] The pharmacokinetics of trimethop-

Table 1 *Trimethoprim pharmacokinetic results in six infants*

Case No	*Age*	*Weight (kg)*	*Dose (mg/kg)*	*Half life (hours)*	*Volume of distribution (l/kg)*	*Plasma clearance (ml/min/kg)*	*Drug*
1	1·7 months	1·59	3·52	5·6	1·7	3·5	Trimethoprim sulphamethoxazole (oral)
2	2·5 months	2·93	1·63	6·1	2·8	5·3	Trimethoprim sulphamethoxazole (intravenous)
3	2·5 months	4·12	0·61	6·0	1·1	2·2	Trimethoprim (oral)
4	3·0 months	4·83	3·66	3·7	1·0	3·0	Trimethoprim sulphamethoxazole (intravenous)
5	1·05 years	8·38	2·98*	3·3	—	—	Trimethoprim (oral)
6	1·08 years	8·55	2·92	3·2	0·7	2·6	Trimethoprim (oral)
Mean	0·49	5·07	2·77	4·6	1·5	3·3	

*Dose swallowed not exactly known.

Table 2 *Mean trimethoprim pharmacokinetic values in newborn babies, children, and adults*

Age group	*Half life (hours)*	*Volume of distribution (l/kg)*	*Plasma clearance (ml/min/kg)*	*Drug*
Newborn babies (n=12)*	19·0	2·7	1·8	Trimethoprim sulphamethoxazole (intravenous)
1·5–3 years (n=7)†	3·8	0·9	2·9	Trimethoprim (oral)
8–10 years (n=9)†	5·4	1·1	2·4	Trimethoprim (oral)
Adults (n=12)†	11·2	1·3	1·4	Trimethoprim (oral)

*Data from Springer *et al*[2]; †data from Hoppu.[3]

rim were investigated in infants falling between these two age groups to serve as a basis for dosage recommendations.

Patients and methods

Six infants were studied during treatment for various infections with either trimethoprim or trimethoprim plus sulphamethoxazole. The drug was administered orally (Trimopan, Farmos Ltd) or intravenously (Bactrim, Hoffman-La Roche). Blood samples were drawn at 0, 1, 3, 6, 9, and 12 hours in cases 2 to 4. The 1 hour sample was omitted for case 1. In cases 5 and 6 blood samples were drawn additionally at 24 hours. In one boy (case 4), who was treated for an infection of his cerebrospinal fluid shunt, samples of cerebrospinal fluid were collected from a ventriculostoma simultaneously with the blood samples.

Concentrations of trimethoprim in serum and cerebrospinal fluid were analysed with high performance liquid chromatography.[4] The method has a wide range of linearity (0·11–690 μmol/l). The accuracy was 99·2% with a coefficient of variation of 6·8%. Pharmacokinetic calculations were made assuming complete absorption and first order kinetics, as described elsewere.[3] Volume of distribution and plasma clearance were not calculated for case 5, as the dose actually swallowed was not known. Results were compared with data from previous studies on newborn babies[2] and children.[3] The difference from children of 1·5 to 3 years was tested with the Mann-Whitney rank sum statistic because of the non-normal distributions. The study protocol was approved by the ethical committee of the hospital.

Results

The tables show data for the patients and individual pharmacokinetic values. The figure shows the half life, volume of distribution/kg, and the plasma clearance/kg in relation to the values found previously for newborn babies, children, and adults.

The mean half life for the infants was 4·6 hours (p=0·39 compared with the control children aged 1·5 to 3 years). The mean volume of distribution for the infants was 1·5 l/kg (p=0·2 compared with children aged 1·5 to 3 years). The plasma clearance of 3·3 ml/min/kg, was faster than has been observed in any other age group (p=0·58 compared with the children aged 1·5 to 3 years).

In case 4 (the infant with a cerebrospinal fluid shunt) the mean ratio of cerebrospinal fluid to serum trimethoprim was 0·43, with a minimum of 0·29 at six hours and a maximum of 0·60 at 12 hours The ratio of the area under the curves for cerebrospinal fluid to serum concentration was 0·36.

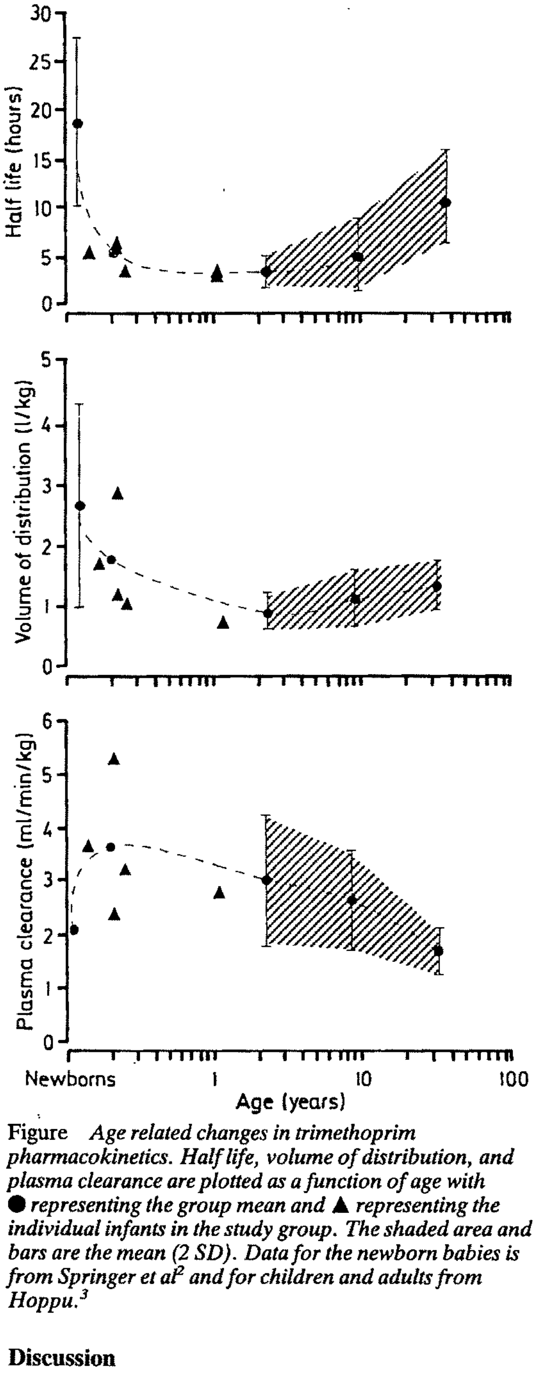


Figure *Age related changes in trimethoprim pharmacokinetics. Half life, volume of distribution, and plasma clearance are plotted as a function of age with ● representing the group mean and ▲ representing the individual infants in the study group. The shaded area and bars are the mean (2 SD). Data for the newborn babies is from Springer et al[2] and for children and adults from Hoppu.[3]*

Discussion

The long half life of trimethoprim in neonates (mean 19·0 hours)[2] shortens during the first two to three months to values comparable with that of school age children.[3] This change is due to both an increase in elimination and a reduction in the volume of distribution. The rapid plasma clearance found in the younger infants was within the 2 SD range for the children 1 to 3 years old, except for patient 2. The half life of trimethoprim seems to be shortest (3·7 hours), the volume of distribution/kg smallest (0·86 l/kg), and the plasma clearance/kg most rapid (2·8 to 3·5 ml/min/kg) during the first three years of life. Thereafter the plasma clearance/kg slowly decreases and the volume of distribution/kg and half life slowly increase to reach adult values around puberty.[3]

There was no evidence of a systematic difference between volume of distribution and plasma clearance values obtained after oral and after intravenous administration, supporting the assumption of complete absorption. The reduction in volume of distribution/kg observed may be due, at least partly, to age related changes in the protein binding of trimethoprim, indicated by Vree *et al.*[5] Neither the renal elimination nor the metabolism of trimethoprim have been studied in newborn babies or infants. In children about 50% of a dose is excreted into the urine unchanged.[3] The change in plasma clearance after the newborn period probably results from more rapid rates of both metabolism and renal elimination. The cerebrospinal fluid:plasma ratio of the trimethoprim concentration and area under the curve were comparable with previous results in children.[1 6]

Similar patterns of age associated changes in pharmacokinetics have been found for various other drugs, for instance gentamycin,[7] theophylline,[8] and ceftriaxone.[9]

A dose of 1 mg/kg of trimethoprim every 12 hours, after a loading dose of 3 mg/kg, is recommended for newborn babies.[2] During the first one to two months of life such a reduced dose seems prudent. Thereafter three daily doses, as recommended for children,[3] seem more appropriate in the light of the plasma clearance and half life values found. The size of the individual dose depends on the infection treated, being usually 2 to 6 mg/kg. These recommendations are based on pharmacokinetic studies; their safety and efficacy must be subjected to further trial.

This study was supported by a grant from the Foundation of Finnish Medical Sciences, Helsinki, Finland.

References

[1] Sabel K-G, Brandberg Å. Treatment of meningitis and septicemia in infancy with a sulphamethoxazole/trimethoprim combination. *Acta Paediatr Scand* 1975;**64**:25–32.

[2] Springer C, Eyal F, Michel J. Pharmacology of trimethoprim-sulfamethoxazole in newborn infants. *J Pediatr* 1982;**100**:647–50.

[3] Hoppu K. Age differences in trimethoprim pharmacokinetics—need for revised dosing in children? *Clin Pharmacol Ther* 1987;**41**:336–43.

[4] Hoppu K, Arjomaa P. Determination of trimethoprim in pediatric samples by high-performance liquid chromatography. *Clin Chim Acta* 1987;**163**:81–6.

[5] Vree TB, Hekster YA, Lippens RJJ. Clinical pharmacokinetics of sulfonamides in children: relationship between maturing kidney function and renal clearance of sulfonamides. *Ther Drug Monit* 1985;**7**:130–47.

[6] Fries N, Keuth U, Braun JS. Untersuchungen zur Liquorgängigkeit von Trimethoprim im Kindesalter. *Fortschr Med* 1975;**93**:1178–83.

[7] Rohwedder HJ, Goll U. Untersuchungen über die Pharmacokinetic von Gentamycin bei Kindern. *Dtsch Med Wochenschr* 1970;**95**:1171–4.

[8] Aranda JV. Maturational changes in theophylline and caffeine metabolism and disposition: clinical implications. In: Lemberger L, Reidenberg MM, eds. *Proceedings of the second world conference on clinical pharmacology and therapeutics.* Rockville Pike: American Society of Pharmacology and Experimental Therapeutics, 1984:868·77.

[9] Hayton WL, Stoeckel K. Age-associated changes in ceftriaxone pharmacokinetics. *Clin Pharmacokinet* 1986;**11**:76–86.

Correspondence to Dr K Hoppu, Children's Hospital, University of Helsinki, Stenbäckinkatu 11, 00290 Helsinki, Finland.

Accepted 13 September 1988

Archives of Disease in Childhood, 1989, **64**, 346–351

Anorexia nervosa and food avoidance emotional disorder

J F HIGGS, I M GOODYER, AND J BIRCH

The Royal Manchester and Booth Hall Children's Hospitals, Manchester

SUMMARY A retrospective and longitudinal study was carried out on all children and adolescents who presented to a child psychiatry service over a period of 26 years to identify the nature, course, and outcome of cases meeting criteria for anorexia nervosa (n=27). Two groups of the same age were identified for comparison, firstly those with food avoidance and emotional disorders (n=23), and secondly those with emotional disorders but no symptoms associated with eating (n=22). The results confirm previous reports that early onset anorexia nervosa shows a similar nature, course, and outcome to the adult disease. Being tall at presentation seems to be associated with a poor outcome. Self starvation of early onset may result in short stature in some cases.

There seem to be more boys among the group in whom the disease was of early onset than would be predicted from the sex ratio among adult patients. In addition boys with anorexia nervosa may have a better prognosis than girls. Children with food avoidance emotional disorders seem to have a worse prognosis than expected for childhood emotional disorders. They may represent a middle group between those with anorexia nervosa and those with emotional disorders but no symptoms associated with eating.

The occurrence of anorexia nervosa in childhood and early adolescence has been known for some time though it has generally been thought to be rare, particularly in prepubertal children.[1–3] Recently, however, there have been a number of reports that have suggested that some children and young adolescents who meet the diagnostic criteria for anorexia nervosa may be missed or diagnosed late[4 5]; that the nature, course, and outcome of the disorder in young people is similar to that of adult patients; and that self starvation of early onset may delay puberty and restrict subsequent physical growth, perhaps permanently.[6 7]

These studies indicate a number of clinical characteristics. The essential characteristics may be identified in children as young as 7 to 8; prepubertal cases do occur infrequently, the clinical picture in prepubertal children may present with varying degrees of emotional and behavioural symptoms; depression is commonly part of the presenting picture; and a larger number of boys may present in childhood than as adults.

In the one longitudinal study[6] a poor prognosis was associated with: early age at onset, a long duration (more than eight weeks) in hospital, two or more admissions to hospital, depression at presentation, and certain adverse family factors—for example, one parent families, step families, and intergenerational families with three or more generations in the house.

In addition to those with classical anorexia nervosa, a number of children present to psychiatric clinics with symptoms associated with eating who are considered to have more general emotional disturbances. Most of these are preschool children although some are in middle childhood. Such cases are commonly classified as childhood emotional disorder (International Classification of Diseases (ICD) 9 code 313.0), occasionally as depression (ICD code 300) and, in the absence of other clear diagnostic criteria as neurotic eating disorder (ICD 9 code 307.5). At present we know little of the similarities or differences between these emotional disorders and anorexia nervosa.

A cross sectional and longitudinal study of cases presenting with anorexia nervosa, and emotional disorders with or without symptoms of food avoidance may provide further evidence about the nature, course, and outcome of disorders associated with food avoidance in young people.

Patients and methods

The study was carried out at the Royal Manchester and Booth Hall children's hospitals, which provide a district and regional service for the north west of England and have a university department of child and adolescent psychiatry as well as inpatient facilities for severely disturbed children and adolescents. All records from 1958 (the inception of the inpatient child psychiatry service) to 1984 were included in the study. The records were searched firstly for all cases who met the diagnostic criteria for anorexia nervosa as set out by Russell.[8]

These criteria were modified to include only those children in whom puberty was not complete and who exhibited behaviour which lead to a marked loss of body weight, or had a morbid fear of becoming fat, or had no evidence of menarche in girls or signs of secondary sexual characteristics in boys. These subjects were identified as the 'early onset anorexia nervosa group' as their disorder occurred in childhood or adolescence and they were prepubertal or were identified as having not completed puberty.

For each case two psychiatric comparison groups were identified who were the same age at referral The first showed a disorder of the emotions in which food avoidance was a prominent symptom in the presenting complaint. The following criteria also had to be met for this group: a history of food avoidance or difficulty such as food fads or restrictions of at least one month; a failure to meet criteria for anorexia nervosa; and the absence of organic brain disease, psychosis, illicit drug abuse, or prescribed drug related causes.

The second comparison group comprised those patients who had disorders of emotions in which the main symptoms included anxiety, together with degrees of fearfulness and panic. Other symptoms such as misery and sadness, obsessionality, and hysterical phenomena could be present but did not dominate the clinical picture. The comparison cases consisted of the next case after the anorexic case who met the above criteria.

DATA FROM CASENOTES

The following data were collected from the casenotes:

(i) Body weight and height; expected body weight was used as a comparison between the clinical groups and taken from standardised centile charts and normal values for the general population.[9–11]

(ii) The past medical and psychiatric history of the child including obstetric and perinatal problems and past developmental difficulties.

(iii) The presence of family adversity. This included medical and psychiatric disorders in nuclear family members, life events including family moves, permanent separations, and disruptions. Disruptive events were defined as those the effects of which were likely to have altered the families' status quo permanently.

(iv) Demographic characteristics and social circumstances at the time of presentation.

FOLLOW UP DATA

Cases of anorexia nervosa and food avoidance were traced through their general practitioners or the National Health Service register. A standardised interview routine was used to evaluate the patients' physical, mental, and social well being.[12] The interview was carried out with the subject and provided for ratings in five areas: nutrition, menstruation, mental state, psychosexual development, and socioeconomic circumstances; these five areas received individual scores. A general outcome score may be calculated based on the previous six months' history of weight and menstrual function in girls and weight alone in boys. General outcome was rated on a 3 point scale: good, moderate, and poor adjustment. All subjects who participated in the follow up study had their height, weight, and pubertal state recorded.

Non-parametric, χ^2 test, and Fisher's exact test were used to assess the significance of differences among the groups, as appropriate.

Results

A total of 8051 records were surveyed. Twenty seven children met the criteria for anorexia nervosa. Twenty three children with predominant (food avoidance) eating difficulties, and 22 with emotional disorders not associated with eating met the criteria for the comparison groups.

All casenotes were surveyed independently by two of the authors (JH and JB) who were unaware of each other's findings. The kappa coefficients ranged from 0·64 to 0·93 for the recorded information indicating satisfactory reliability.

CLINICAL AND BACKGROUND CHARACTERISTICS OF THE THREE GROUPS

The characteristics of the clinical groups are shown in table 1. Eight of 27 of the cases of anorexia nervosa (30%) were boys. Percentage body weight was calculated and less than 80% body weight considered as indicating wasting. Nineteen of 27 (70%) of those with anorexia nervosa were significantly wasted at the time of presentation compared with six of 19 (32%) of the food avoidance group (χ^2=6·76, df=1, $p<0·01$). Four of eight (50%) of the boys and 15 of 19 (79%) of the girls with anorexia nervosa were wasted (NS). Of the wasted

Table 1 *Comparison of characteristics recorded in the casenotes of the clinical groups at the time of presentation to psychiatric services*

	No with anorexia nervosa (n=27)	*No with eating difficulties (n=23)*	*No with emotional disorders (n=22)*
Sex F:M (%)	19:8 (70:30)	18:5 (78:22)	13:9 (59:41)
Mean age (range) at onset (years)	12 (8–16)	10 (8–14)	10 (7–14)
No (%) below 80% expected body weight for height	19 (74) (15F:4M)	6 (32) (n=19)	0*
No (%) at 3rd centile or less for height and weight	3 (11)	3 (16) (n=19)	0
No (%) 'middle class'	14 (54)	5 (23)	4 (18)*
No (%) giving history of illness in the family	9 (38)	11 (52)	15 (68)*
No (%) giving history of one or more disruptive life events	13 (52)	8 (36)	5 (23)*
No (%) of children with history of obsessionality	16 (59)	4 (17)	2 (9)†

*$p<0{\cdot}05$; †$p<0{\cdot}001$.

subjects three of 19 (16%) in the group with anorexia nervosa compared with half the food avoidance group had heights below the 3rd centile at the time of presentation ($p<0{\cdot}05$).

Comparison of the rest of the data from the casenotes indicated the following significant differences between the groups: cases of anorexia nervosa were significantly more likely than either of the other two clinical groups to have a middle class background ($p<0{\cdot}05$); cases of anorexia nervosa were significantly more likely to have a past history of obsessionality recorded at the time of presentation ($p<0{\cdot}05$), and there was a suggestion in the notes that disruptive life events that permanently altered the families' status quo were significantly more likely in anorexia nervosa families than in the other two groups ($p<0{\cdot}05$).

By contrast, however, a history of medical illness in the family that had required hospital treatment was significantly more likely in emotionally disordered children with no eating symptoms than the group with anorexia nervosa ($p<0{\cdot}05$). No such difference existed, however, between the anorexia nervosa and food avoidance groups, or the food avoidance and emotionally disordered groups.

There were no significant differences among the three clinical groups in family size, the presence of step parents, three or more generations in the same house, or the proportion of adults or siblings with recorded psychiatric disorders, neither were there any significant differences in the obstetric, perinatal, or developmental histories among the three groups.

OUTCOME OF THE FOLLOW UP STUDY

A follow up study was carried out on the 50 children with anorexia nervosa or eating disorders. A letter was written to each family requesting an interview with the identified subject and the parents.

The mean follow up time from discharge from hospital for anorexia nervosa patients was 5·2 years (median 3 years, range 1–26) and for food avoidance cases 6·5 years (median 5 years, range 1–17). The mean age at follow up was 19·3 (12–42) years for the cases with anorexia nervosa and 18·7 years (11–23) for those with food avoidance.

At the time of follow up eight of 27 (30%) anorexia nervosa cases and six of 23 (21%) emotionally disordered cases were less than 16 years old.

All subjects were traced and contacted. Two children had died by the time of follow up, both from the food avoidance group; they were a girl with persistent psychogenic vomiting who had a cardiac arrest, and a boy who was subsequently diagnosed as having muscular dystrophy. Two further boys who had been diagnosed as having anorexia nervosa were found to have physical disease 24 months or later than the original presentation; one had coeliac disease and the other myasthenia gravis. We did not, however, have positive evidence at follow up that their anorexic illnesses had been misdiagnosed, and they were both therefore included in the follow up study.

There was considerable reluctance in both groups on the part of the parents and the subjects to participate in the follow up interviews. In 13 cases (26%) direct interview and examination were refused. Subjects were therefore seen and interviewed in 35 of 50 of the cases (70%). Parents were interviewed in two other cases. In four further cases information was obtained by letter indicating the weight and menstruation pattern over the past six months; this information was used when comparing general outcome between anorexia nervosa and food avoidance groups at follow up. Only results from the direct interviews were used for the comparison of outcome at follow up on all five Morgan-Russell scales.[12] Outcome scores on the Morgan-Russell scales for subjects and parents (that is 35 pairs) obtained at interview showed good agreement ($\text{rho}=0{\cdot}82$ $p<0{\cdot}001$).

Outcome and gender—The general outcome according to gender is shown in table 2. In the anorexia nervosa group, 16 of 19 of the girls (84%) and seven of eight of the boys (88%) were interviewed. Of these, half of the girls were rated as having a poor outcome compared with one of eight of the boys (12·5%) ($p=0·08$). In the food avoidance group 15 of 18 of the girls (83%) and three of five of the boys (60%) were interviewed. Of these three of 15 of the girls (20%) were rated as having a poor outcome and none of the boys (NS).

At the time of follow up one girl in the anorexia nervosa group met the criteria for food avoidance, and three girls in the emotionally disordered group met the criteria for anorexia nervosa. No such diagnostic changes were apparent among the boys.

Short stature at presentation and outcome—Subjects' heights at follow up were compared with norms supplied by the survey of heights and weights of adults in Great Britain.[11] Overall a poorer outcome was significantly more likely in children with anorexia nervosa who were taller at presentation ($p<0·05$). At follow up five of 23 anorexia nervosa subjects (22%) had heights that were less than two standard deviations from the norm for their age. Only one of these cases was short at presentation. For the four food avoidance cases there was no association between height at presentation and poor outcome. Only one case of food avoidance at follow up had a height less than two standard deviations below the norm. There were no significant differences in the length of follow up time between cases with short stature and those of normal height in either clinical group.

Weight at presentation and outcome—Of the 19 cases who were clinically wasted at presentation, six (32%) were rated as having had a good outcome, four (21%) as having had an intermediate outcome and seven (37%) as having had a poor outcome, with three (20%) in whom the outcome was not known. Outcome was therefore not significantly related to being wasted at presentation.

Association between background factors and outcome—There were no significant associations between poor outcome for either clinical group at follow up and any of the following background factors: presence of depression at presentation, age at onset, social class, family size, divorced parents, ordinal position of the child, length of stay in hospital, inpatient treatment, or multiple admissions to hospital. Obsessional features at presentation were, however, significantly more common among those with anorexia nervosa who had poor outcomes.

Association between clinical features at follow up and outcome—The relative contribution of the five Morgan-Russell subscales to the general outcome score for both clinical groups is shown in table 3. For cases of anorexia nervosa the contribution to poor outcome derives from all five subscales (nutritional status, menstruation, mental state, psychosexual, and socioeconomic). The trend of scores for the subscales for eating difficulties suggests that poor outcome is associated with all subscales except psychosexual.

Finally, there were no significant differences at follow up in any of the findings for children who presented above or below 12 years of age in any of the clinical groups.

Discussion

This study provides confirmation that anorexia nervosa does occur in young people before the onset of puberty. In this sample the youngest patient was 8 years of age at presentation suggesting that her disorder may have started some months before she was 8. No study has yet reported the onset of anorexia nervosa before the age of 7.

The cross sectional results are of some interest, but their interpretation must be conservative because

Table 2 *Number (%) of patients with anorexia nervosa (n=23) and food avoidance emotional disorders (n=18) who had good, intermediate, or poor outcomes at follow up according to the Morgan-Russell general outcome scale*

	Good outcome		*Intermediate outcome*		*Poor outcome*	
	Anorexia nervosa (n=7)	*Food avoidance emotional disorders (n=11)*	*Anorexia nervosa (n=7)*	*Food avoidance emotional disorders (n=4)*	*Anorexia nervosa (n=9)*	*Food avoidance emotional disorders (n=3)*
Boys	2 (29)	3 (27)	4 (57)	0	1 (11)	0
Girls	5 (71)	8 (73)	3 (43)	4 (100)	8 (89)	3 (100)

Table 3 *Mean scores of the Morgan-Russell subscales for the general outcome for anorexic (n=18) and food avoidance emotional disorder (n=17) groups**

	Good outcome		*Moderate outcome*		*Poor outcome*	
	Anorexia nervosa (n=5)	*Food avoidance emotional disorders (n=10)*	*Anorexia nervosa (n=6)*	*Food avoidance emotional disorders (n=4)*	*Anorexia nervosa (n=7)*	*Food avoidance emotional disorders (n=3)*
Nutrition	10·6	10·2	5·5	5·7	4·0	3·3
Menstrual function	11·0	10·4	6	9	1·3	2·7
Mental state	11·2	10·8	8·7	7	8	5·3
Psychosexual	10·8	11·4	6·3	7·5	5·7	9·5
Socioeconomic	9·8	9·6	9·4	7·9	7·2	3·0

*Based on direct interview of 35 subjects.

of the well known problems of the reliability and validity of retrospective collection of data from casenotes. We used comparison groups in an attempt to minimise any overemphasis of associations that may have been present between cases of anorexia nervosa and individual and family information at the time of presentation.

The lack of any significant differences among the groups in terms of family structure therefore suggests that such factors hold no specific meaning in anorexia nervosa. Of some interest, however is the suggestion that life events that disrupt family life and permanently alter the families' status quo are significantly more common in anorexic families than emotional disorders without food avoidance but not those presenting with food avoidance. The trend of the results suggests that children identified as having food avoidance emotional disorders but who do not meet the criteria for anorexia nervosa seem to have an intermediate disorder (between anorexia nervosa and food avoidance) on the background characteristics we examined. We know of no studies that have examined the psychopathology of eating in childhood. We therefore cannot be sure of the nature of these cases. The recent reporting of a partial syndrome of anorexia nervosa[13] where there are some, but not all, of the criteria for diagnosis suggests that in some cases eating difficulties in childhood may reflect a more serious psychopathological issue than has hitherto been considered.

Results of the follow up study suggested that the overall outcome for children with anorexia nervosa is not good. In this study the nature, course, and outcome of early onset anorexia nervosa were similar to those of adult cases.[14]

The follow up interviews suggested that some of the subjects remained preoccupied about food and weight in general although they no longer met the criteria for anorexia nervosa. For example, one man in his late 20s had become concerned that his 9 month old son was becoming fat even though there was no evidence for this. Perhaps recovered anorexics return to a pool of the population who have abnormal concerns about weight and food.

A further finding was that the outcome may be somewhat better for boys than girls; the reasons for this are not clear. There were no important differences between the sexes in any of the variables relating to presentation or outcome. Our social measures are of course substantially restricted by the study design. Perhaps this and the intrinsic psychological and physiological differences between boys and girls may account for the differences in overall outcome. The suggested finding and subsequent interpretation require further investigation.

Two boys were diagnosed as having physical disorders after initial treatment for anorexia nervosa. Clearly the misdiagnosis of a treatable physical disorder such as coeliac disease should be avoided. It should not be assumed, however, that the presence of such a diagnosis precludes a concurrent psychiatric syndrome related to food avoidance. For example, anorexia nervosa has been reported in the presence of cystic fibrosis and its occurrence in adults with diabetes mellitus has often been noted.[15]

The associations between weight and height are of interest. Being tall at presentation seems to indicate a poorer outcome at follow up. It may be that being taller at presentation sensitises these children to concerns about their body image. There is also the suggestion that it is the continued presence of self starvation that is producing short stature in some adults with early onset anorexia nervosa. These findings emphasise again the critical clinical issue of reinstituting a normal diet in young patients with anorexia nervosa.

The methodological limitations of this longitudinal study require some comment. Firstly, the length of follow up is variable. Secondly, there are differences in rate of development at the time follow up interview; both these factors may influence the outcome scores. Poor outcome, however, was not correlated with the duration of follow up time, but nevertheless these findings must be interpreted with caution.

Bryant-Waugh *et al*[6] reported a number of background factors associated with poor outcome among children with early onset anorexia nervosa. These include family factors (one parent families, step parents, and three or more generations living in the same house), depression in the child at presentation, long or multiple admissions to hospital (or both), and a younger age of onset. None of these factors, however, are significantly associated with poor outcome in anorexia nervosa cases in this study.

Clinical findings in the follow up subjects indicate that obsessionality at presentation was associated with a poor outcome for cases of anorexia nervosa but depression at presentation was not. These findings are not surprising in view of the evidence that suggests that obsessional symptoms in children show pronounced continuity into adult life.[16] This suggests a rather non-specific but adverse role for obsessional features in anorexia nervosa. There seems to be no increased risk to the overall outcome for children whose onset of disorder is below the age of 12. Age 'cut off' is not the same as investigating the effects of puberty. Nevertheless, the results suggest little influence of puberty on the outcome.

The natural course and outcome for food avoidance emotional disorders seems more uncertain than would be predicted from a diagnosis of childhood emotional disorder with anxiety and fearfulness. Their overall outcome, however, seems to be better than that of early onset anorexia nervosa. Some of these patients may have been depressed, and some may represent the partial syndrome of anorexia nervosa recently described in reports of adult onset disorders.

We thank Professors Gerald Russell and Gethin Morgan for their assistance at various stages of this project. Both Professor Russell and Dr Peter Cooper provided invaluable comments during the preparation of this manuscript.

References

[1] Blitzer J, Rollins N, Blackwell A. Children who starve themselves: anorexia nervosa. *Psychosom Med* 1961;**23**:369–83.

[2] Lesser L, Ashenden BJ, Debuskey M, Eisenberg L. Anorexia nervosa in children. *Am J Orthopsychiatry* 1960;**30**:572–80.

[3] Warren W. A study of anorexia nervosa in young girls. *J Child Psychol Psychiatry* 1968;**9**:27–40.

[4] Jacobs B, Isaacs S. Pre-pubertal anorexia nervosa: a retrospective controlled study. *J Child Psychol Psychiatry* 1986;**27**:237–50.

[5] Fosson A, Knibbs J, Bryant-Waugh R, Lask B. Early onset anorexia nervosa. *Arch Dis Child* 1987;**62**:114–8.

[6] Bryant-Waugh R, Knibbs J, Fosson A, Kaminski Z, Lask B. Long term follow up of patients with early onset anorexia nervosa. *Arch Dis Child* 1988;**63**:5–9.

[7] Russell GFM. Delayed puberty due to anorexia nervosa of early onset. In: Darby PL, Garfinkel PE, Garner DM, Coscina DV, eds. *Anorexia nervosa: recent developments in research.* New York: Alan R Liss, 1983:331–42.

[8] Russell GFM. Anorexia nervosa: its identity as an illness and its treatment. In: Price JH, ed. *Modern trends in psychological medicine.* London: Butterworth, 1970:131–62.

[9] Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity, and weight velocity: British children 1965, part I. *Arch Dis Child* 1966;**41**: 454–71.

[10] Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity: British children 1965, part II. *Arch Dis Child* 1966;**41**: 613–5.

[11] Rosenbaum S, Skinner PK. A survey of heights and weights of adults in Great Britain in 1980. *Ann Hum Biol* 1985;**1**:1–22.

[12] Morgan HG, Russell GFM. Value of family background and clinical features as predictors of long-term outcome in anorexia nervosa: a follow up study of 41 patients. *Psychol Med* 1975;**5**:355–71.

[13] Mann AH, Wakeling A, Wood U, Monke E, Dobbs L. Screening for abnormal eating attitudes and psychiatric morbidity in an unselected population of 15 year old schoolgirls. *Psychol Med* 1983;**13**:573–80.

[14] Hsu LK. Outcome of anorexia nervosa: a review of the literature. *Arch Gen Psychiatry* 1980;**37**:1041–6.

[15] Szmuckler GI. Anorexia nervosa and bulimia in diabetics. *J Psychosom Res* 1984;**28**:365–9.

[16] Zeitlin H. *The natural history of psychiatric disorder in children.* Maudsley monographs, No 29. Oxford: Oxford University Press, 1986.

Correspondence to Dr IM Goodyer, Department of Psychiatry, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 2QQ.

Accepted 5 September 1988

Archives of Disease in Childhood, 1989, 64, 352–356

Blood selenium concentrations and glutathione peroxidase activity

B LLOYD,* E ROBSON,* I SMITH,† AND B E CLAYTON*

**University Unit of Chemical Pathology and Human Metabolism, Southampton General Hospital, Southampton, and †Institute of Child Health, London*

SUMMARY Selenium concentrations in children and teenagers without a metabolic disorder eating normal diets (group 1), and young patients with classical phenylketonuria and milder forms of hyperphenylalaninaemia being treated with a diet low in natural protein (group 2) were investigated. There was a strong correlation between blood selenium concentration and age in children in group 1 up to 10 years of age. Blood selenium concentrations and glutathione peroxidase activities were significantly lower in the patients who were receiving diets containing reduced amounts of natural protein, and the differences were more than would be expected for age. When the concentrations of selenium in blood from groups 1 and 2 were compared with glutathione peroxidase activity, a strong association was found when blood selenium concentrations were below 1·26 μmol/l. Reduction in glutathione peroxidase activity may be harmful in the long term, and the addition of selenium to therapeutic diets is recommended.

Selenium exists naturally in food mainly as organic compounds such as the amino acids selenomethionine, selenocystine, and selenocysteine.[1] The estimated dietary intakes of selenium in different countries vary considerably, resulting in wide divergence in blood selenium concentrations.[2] Dietary intakes within the range 50–200 μg/day (0·63–2·53 μmol) are considered adequate and safe for adults,[3] and Thorn *et al*[4] reported an average intake of 60 μg/day (0·76 μmol) in the United Kingdom. The safe and adequate intake from 0 to 6 years varies with age within the range 10–120 μg,[5] but Lombeck *et al* noted that the selenium content of infant formulas based on cows' milk were lower than those of human or cows' milk samples.[6] They concluded that infants receive between 3·5–13·3 μg/day of selenium according to the feed given. Severe reduction in intake of selenium in the general population in Britain does not occur, unlike some countries such as China.[7]

Selenium is an essential component of the enzyme glutathione peroxidase (EC 1.11.1.9), which functions as part of an antioxidant system to protect membranes and essential proteins from the potentially damaging effects of reactive oxygen and lipid peroxides.[8] The intake of this element is therefore particularly important when considering therapeutic diets, parenteral nutrition, and the increasing intakes of convenience foods. Children with the more severe forms of hyperphenylalaninaemia,[9] mainly classical phenylketonuria, receive a synthetic substitute in place of much of the natural dietary protein and therefore provide a suitable group in which to study the association between blood selenium concentrations and glutathione peroxidase activity. The synthetic protein substitutes are low in or free from selenium, which is also not included in the trace element supplements prescribed with such diets.

In this study the association between glutathione peroxidase activity and blood selenium concentrations was assessed in a wide range of measurements, firstly in order to determine the blood selenium concentration at which glutathione peroxidase activity is reduced in children. Secondly, we believe that the information provided will be useful when considering supplementation with selenium in synthetic diets. The subjects included children and teenagers (without metabolic disorders) receiving normal food as well as patients of varying degrees of severity who were receiving phenylalanine controlled diets.

The study had the approval of the joint ethical subcommittee of the Southampton and South West

Hampshire Health Authority and the University of Southampton.

Subjects and methods

Group 1 comprised children and teenagers (without metabolic disorders) eating normal diets. As it is difficult to justify taking blood samples by venepuncture or finger prick from healthy children without a medical reason, we used specimens that had already been collected for other analyses. The samples were obtained from the following sources: Group 1a: local out patients (n=59) at Southampton General Hospital, having routine haematological investigations for minor ailments. Group 1b: samples received at the hospital (n=24) from many hospitals throughout the United Kingdom for routine measurement of blood lead concentrations. None of the specimens in this group had blood lead concentrations of more than 1·0 μmol/l. Group 1c: blood samples from children in Greenwich (n=20) which had formed part of an environmental project and were no longer required for further analysis. Group 1d: blood samples from children in inner London (n=38), part of the same environment project.

Group 2 comprised children and teenagers with classical phenylketonuria and milder forms of hyperphenylalaninaemia. As it is customary to monitor the blood phenylalanine concentrations of patients with phenylketonuria or milder forms of hyperphenylalaninaemia at regular intervals, whether they are on a strict or free diet, a few extra drops of blood obtained by finger prick or heel prick were collected for this study provided consent had been given. The blood samples were therefore obtained from patients attending clinics at Southampton (group 2a, n=16) as well as the Hospital for Sick Children, Great Ormond Street, London (group 2b, n=42).

Whole blood samples were stored at −20°C until analysis. Selenium was assayed by hydride generation and atomic absorption spectrophotometry,[10] and the activity of glutathione peroxidase was measured within seven days of collection of the samples by the method of Beutler[11] using t-butyl hydroperoxide as substrate. Only a limited number of specimens were suitable for glutathione peroxidase analysis as many of the specimens were too old, or too small.

The Mann-Whitney U test and regression analysis of the data were carried out on an IBM PC using the EPISTAT statistical package.

Results

The results for the children and teenagers in group 1 are shown in table 1. The mean blood selenium concentrations and glutathione peroxidase activities were similar for subjects in group 1a and group 1d. Group 1b, however, had a lower mean selenium concentration and group 1c had a higher mean selenium concentration.

Because the mean ages and the age ranges of the subjects in the four groups varied considerably, a possible association between selenium concentration and age was studied by regression analysis, and the coefficient of correlation (r) was 0·46. The data were then reanalysed for children above and below 10 years of age. Fig 1 shows an increase in blood selenium concentration (r=0·56) in children under 10 years old, but in the older subjects (10 to 19 years) there was no correlation between selenium and age (r=0·04).

Details of the patients in groups 2a and 2b together with their results are given in table 2. The data were analysed according to diet and hospital. Blood selenium was significantly higher (p<0·01) in the free diet groups from both hospitals (p<0·001) than in the strict diet groups from either hospital.

Table 1 *Selenium concentrations in children in group 1*

Group No	*Sample source*	*Mean (range) age (years)*	*Mean (SD) blood selenium concentration (μmol/l)*	*Mean (SD) glutathione peroxidase activity (U/g Hb)*
1a	Southampton	13·1 (4–19)	1·33 (0·24) (n=59)	16·8 (3·1) (n=42)
1b	Southampton*	2·3 (0·7–4)	0·99 (0·27) (n=24)	Not measured
1c	Greenwich	8·2 (3–15)	1·47 (0·26) (n=20)	Not measured
1d	Inner London	6·7 (6–7)	1·28 (0·14) (n=38)	16·5 (3·5) (n=31)

*Blood samples analysed at Southampton General Hospital but received from many different towns.

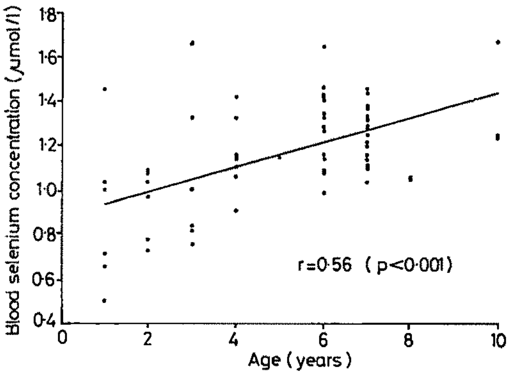


Fig 1 *Correlation between blood selenium concentration and age in healthy children.*

Glutathione peroxidase activities showed a similar pattern.

In order to assess the possible association between blood selenium concentrations and glutathione peroxidase activity, all the available results from patients in group 2 were combined with those of the subjects on a normal diet (group 1) to give a wide range of selenium concentrations. The complete data were first tested by regression analysis and gave a correlation coefficient of 0·63, then reanalysed taking blood selenium values below and above 1·26 µmol/l separately. Fig 2 shows a good correlation between blood selenium concentrations and glutathione peroxidase activity when blood selenium concentrations were less than 1·26 µmol/l (r=0·77,

Table 2 *Blood selenium concentrations glutathione peroxidase activity in relation to diet for patients in group 2*

Group No	*Hospital*	*Diet*	*Mean (range) age (years)*	*Mean(SD) blood selenium concentration (µmol/l)*	*Mean(SD) glutathione peroxidase activity (U/g Hb)*
2a	Southampton General Hospital:	Free	15·3 (11–18)	*1·47 (0·37) (n=4)	*14·3 (2·6) (n=3)
2b	Hospital for Sick Children:	Free	6·3 (0·66–17)	**1·26 (0·59) (n=9)	**11·3 (2·6) (n=6)
		Strict	2·1 (0·09–8)	0·56 (0·23) (n=33)	7·3 (2·6) (n=19)

*Blood selenium concentrations and glutathione peroxidase activities were significantly higher in the patients on a free diet compared with those on a strict diet.
*p<0·01; **p<0·001.

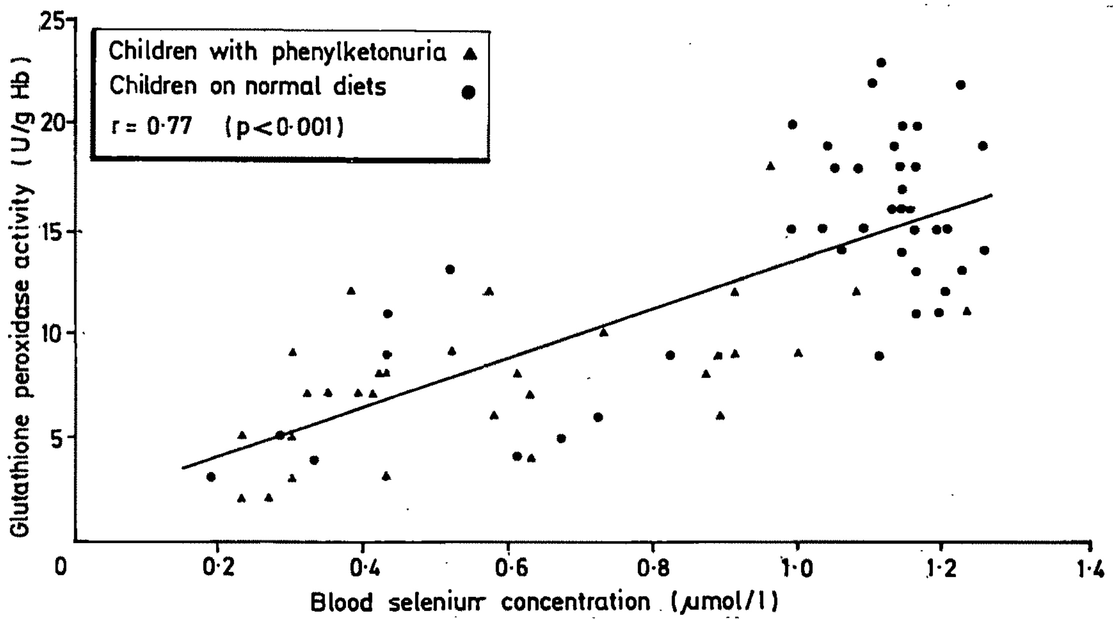


Fig 2 *Correlation between blood selenium concentrations and glutathione peroxidase activities in children with phenylketonuria and those on normal diets.*

$p<0.001$). Above this concentration there was no correlation between blood selenium concentration and enzyme activity ($r=-0.16$).

Discussion

The concentrations of selenium in blood from subjects eating normal food varied considerably. The differences may be solely a result of age, but different foods and ethnic backgrounds may have had an effect as a number of children were of Asian origin.

It has previously been reported that the lowest concentrations of serum selenium in healthy people have been found in infants 1–4 months old and that they increase thereafter with age until adult concentrations are reached.[6–12] Modern practice is to feed infants with processed food rather than a home prepared diet, but information about the selenium content of processed infant food is limited.[13] Morris and Levander,[14] however, showed that processing caused a 40–50% reduction in the selenium content of strained infant food. In this study the upward trend in selenium concentration did not continue after 10 years of age, and may show that by this age the diet of the children was similar to that of adults, although Ward *et al*[15] in an earlier study reported that adult levels of blood selenium seemed to have been achieved by the time the children were 5 or 6 years old.

Significant differences were found when blood selenium concentrations of patients with hyperphenylalaninaemia from both hospitals were compared according to diet. Generally patients on free diets were much older than those on a strict diet; however, the difference in selenium concentrations between the two groups was more than would be expected for age when compared with subjects on a normal diet. The low blood selenium concentrations and glutathione peroxidase activities of the children on strict diets were similar to those previously reported in areas of China where Keshan disease, an endemic cardiomyopathy, was common.[16] Four children on strict diets were therefore examined by echocardiography but no abnormalities were seen. It has previously been reported that glutathione peroxidase activity in children with phenylketonuria controlled by diet and given selenium supplementation in the form of selenium yeast only achieved normal concentrations after 80–100 days of supplementation.[12] As yet no long term studies of selenium supplementation in children receiving synthetic diets have been reported as far as we know.

The enzyme requires the presence of selenocysteine in the active site[17 18] and both experimental and clinical selenium deficiency have been shown to result in decreased glutathione peroxidase activity.[19] In vitro kinetic measurements of glutathione peroxidase activity are unable to distinguish between an inactive enzyme and a lack of enzyme protein. Takahashi *et al*[20] recently developed a polyclonal monospecific antibody that was used to show a direct association between glutathione peroxidase activity and protein content in the red cells of both normal and selenium deficient subjects. They suggested that there may be an association between selenium and synthesis of glutathione peroxidase protein, as a deficiency in selenium would result in a deficiency of selenocysteine required for the production of enzyme protein.[21] Carmagnol *et al* reported that a high proportion of glutathione peroxidase activity found in hepatic, renal, and skeletal muscle of human tissue is not selenium dependent. Glutathione peroxidase activity in human erythrocytes, however, and more importantly in cardiac tissue, contains only the selenium dependent form of the enzyme.[22]

Clinical management of the more severe forms of hyperphenylalaninaemia is dependent on dietary treatment. It is therefore unfortunate that in limiting phenylalanine intake, natural protein intake—and therefore dietary selenium intake—are severely limited too. As selenium is required for the production of glutathione peroxidase protein, children on strict diets may have reduced antioxidant function as a result of reduced enzyme activity. Because the children are given daily vitamin supplements the vitamin E concentrations may be adequate to spare the selenium requirement under normal circumstances. If, however, the children were subject to severe or prolonged oxidative stress, then the vitamin E concentrations might be inadequate to cope with the extra antioxidant requirement.

Until recently it was customary to permit children to relax their diets after about 9 years of age, but it is now believed that a stricter diet should be maintained until the child is older, and possibly throughout life. The period of time that these children and young adults are at risk of damage from antioxidant stress is therefore likely to increase. It has been suggested that older patients with cystic fibrosis have an increased risk of developing carcinoma that is associated with lower concentrations of selenium in serum, particularly in the presence of reduced concentrations of vitamin E.[23] Patients with phenylketonuria may be similarly at risk.

In view of the low concentrations of selenium found in this study, consideration should be given to the addition of selenium to strict therapeutic diets including those used in the treatment of classical phenylketonuria. This would require careful study to prevent selenium toxicity and ensure satisfactory bioavailability.

We thank Dr B Keeton, consultant paediatric cardiologist, for examining the four children with phenylketonuria by echocardiography.

References

[1] Olsen OE, Novacek EJ, Whitehead EI, Palmer IS. Investigations on wheat. *Phytochemistry* 1970;**9**:1181–8.

[2] Thorling EB, Overvad K, Geboers J. Selenium status in Europe–human data. A multicentre study. *Ann Clin Res* 1986;**18**:3–7.

[3] Committee on Dietary Allowances, Food and Nutrition Board. *Recommend dietary allowances*. 9th ed. Washington: National Academy of Sciences, 1980;162–3.

[4] Thorn J, Robertson J, Buss DH. Trace nutrients. Selenium in British food. *Br J Nutr* 1978;**39**:391–6.

[5] Diplock AT. Trace elements in human health with special reference to selenium. *Am J Clin Nutr* 1987;**45**(suppl):1313–22.

[6] Lombeck I, Kasperak K, Harbisch HD, Feinenedegen LE, Bremer HJ. The selenium state of children. 1. Serum selenium concentration at different ages; activity of glutathione peroxidase of erythrocytes at different ages; selenium content of food of infants. *Eur J Pediatr* 1977;**125**:81–8.

[7] Keshan Disease Research Group of the Chinese Academy of Sciences. Epidemiological studies on the etiological relationship of selenium and Keshan disease. *Chin Med J* 1979;**92**:477–82.

[8] Chow CK. Nutritional influences on cellular antioxidant defense systems. *Am J Clin Nutr* 1979;**32**:1066–81.

[9] Smith I. The hyperphenylalaninaemias. In: Lloyd JK, Scriven CR, eds. *Genetic and metabolic disease*. London: Butterworths, 1986;166–210.

[10] Lloyd B, Holt P, Delves HT. Determination of selenium in biological samples by atomic absorption spectroscopy. *Analyst* 1982;**107**:927–33.

[11] Beutler E. *A manual of biochemical methods: glutathione peroxidase (GSH-Px)*. 2nd ed. New York: Grune and Stratton, 1979:71–3.

[12] Lombeck I. The evaluation of selenium state in children. *J Inherited Metab Dis* 1983;**6**(suppl):83–4.

[13] Ebert KH, Lombeck I, Kasperak K, Feinendegen LE, Bremer HJ. The selenium content of infant food. *Z Ernahrungswiss* 1984;**23**:230–6.

[14] Morris VC, Levander OA. Selenium contents of foods. *J Nutr* 1970;**100**:1383–8.

[15] Ward KP, Arthur JR, Russell G, *et al.* Blood selenium content and glutathione peroxidase activity in children with cystic fibrosis, coeliac disease, asthma and epilepsy. *Eur J Pediatr* 1984;**142**:21–4.

[16] Chen X, Chen X, Yang G, *et al.* Relation of selenium deficiency to the occurrence of Keshan disease. In: Spallholz JE, Martin JL, Ganther HE, eds. *Selenium in biology and medicine*. Westport: AVI Publishing, 1981:171–5.

[17] Ganther HE, Hafeman DG, Lawrence RA, Serfass RE, Hoekstra WG. Selenium in health and disease – a review. In: Prasad AS, ed. *Trace elements in human health and disease*. Vol 2. New York: Academic Press, 1976:165–234.

[18] Prohaska J, Oh SH, Hoekstra WG, Ganther HE. Glutathione peroxidase: inhibition by cyanide and release of selenium. *Biochem Biophys Res Commun* 1977;**74**:64–71.

[19] Lombeck I, Kasperak K, Harbisch HD, *et al.* The selenium state of children. II. Selenium content of serum, whole blood, hair and the activity of erythrocyte glutathione peroxidase in dietetically treated patients with phenylketonuria and maple-syrup-disease. *Eur J Pediatr* 1978;**128**:213–23.

[20] Takahashi K, Newburger PE, Cohen HJ. Glutathione peroxidase protein: absence in selenium deficiency states and correlation with enzyme activity. *J Clin Invest* 1986;**77**:1402–14.

[21] Takahashi K, Cohen HJ. Selenium-dependent glutathione peroxidase protein and activity: immunological investigations on cellular and plasma enzymes. *Blood* 1986;**68**:640–5.

[22] Carmagnol F, Sinet PM, Jerome H. Selenuim-dependent and non-selenium dependent glutathione perioxidases in human tissue extracts. *Biochim Biophys Acta* 1983;**759**:49–57.

[23] Stead RJ, Redington AN, Hinks LJ, Clayton BE, Hodson ME, Batten JC. Selenium deficiency and possible increased risk of carcinoma in adults with cystic fibrosis. *Lancet* 1986;**ii**:862–3.

Correspondence to Dr B Lloyd, Faculty of Medicine, Southampton General Hospital, Southampton SO9 4XY.

Accepted 26 August 1988

Archives of Disease in Childhood, 1989, **64,** 357–359

Seizures presenting as apnoea

Y NAVELET,* C WOOD,† I ROBIEUX,† AND M TARDIEU‡

**Service d'Explorations Fonctionnelles du Système Nerveux, †Unité de Réanimation Pédiatrique, ‡Unité de Neuropédiatrie, Centre Hospitalier de Bicêtre, Kremlin Bicetre Cedex, France*

SUMMARY Between the ages of 3 and 6 months a baby boy presented with repeated, non-specific episodes of cyanosis, apnoea, bradycardia, and abnormal movements of the limbs. The episodes were severe and required resuscitation and several admissions to hospital. Initial investigations showed only signs of oesophagitis. Despite treatment of the oesophagitis the symptoms recurred, and electroencephalography and polygraphy eventually showed evidence of minor seizures. Severe epilepsy with tonic-clonic seizures developed when he was 6 months old.

Convulsive disorders in infants can be difficult to diagnose. Initial symptoms sometimes mimic airway obstruction, vagal hyperactivity, or cardiac or digestive problems.

We report the case of an infant who had repeated, non-specific life threatening episodes of prolonged apnoea that were eventually diagnosed as seizures.

Case report

A baby boy was born at full term weighing 3950 g. He had an Apgar score of 8 at one minute, and 10 at five minutes. At the age of 3 months he had a sudden episode of respiratory obstruction with cyanosis, bradycardia, and hyperactive movements

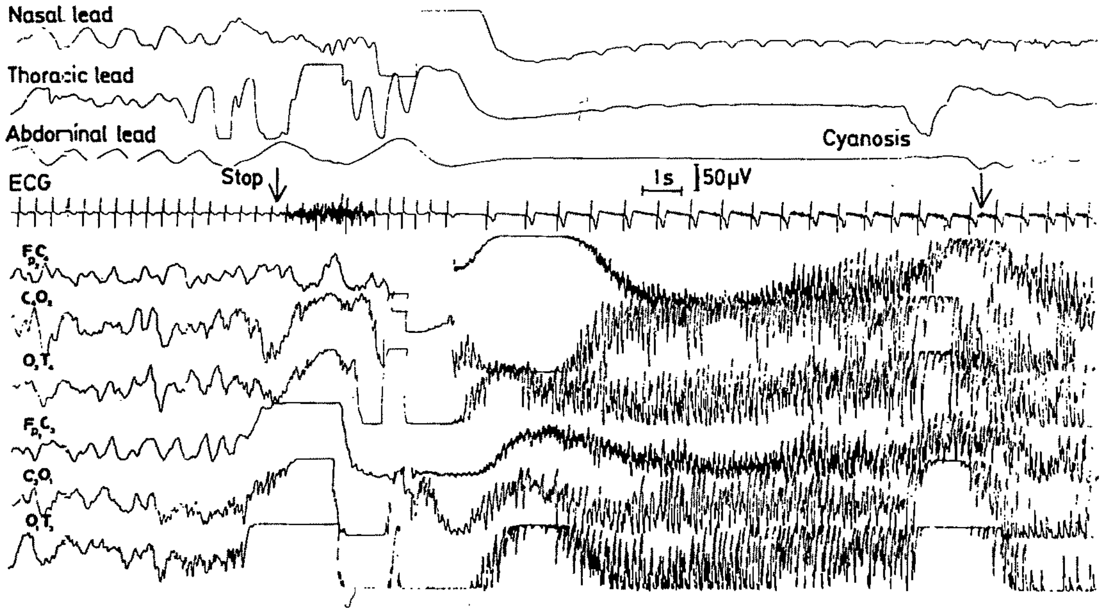


Fig 1 *Seizure triggered by milk feed. Feeding was stopped at the first arrow. Oxygen was given by mask after the second arrow. Respiratory obstruction is recorded on the three respiratory leads (nasal, thoracic, and abdominal). Electroencephalographic discharge starts in the left occipital area with secondary generalisation. Short bradycardia is seen on the electrocardiogram lead.*

of the upper limbs. During his hospital stay three identical episodes occurred that all required cardiopulmonary resuscitation. Neurological examination showed no abnormality. Examination of the cerebrospinal fluid, electroencephalography, 24 hour polygraphy, ultrasonography, and computed tomography were all normal. Hyperactive vagal reflexes were diagnosed; short episodes of bradycardia (heart rate 60/minute) followed ocular compression, and further episodes were recorded during continuous monitoring. Oesophagoscopy showed oesophagitis.

The child was discharged taking antacids and metoclopramide, and his mother was advised to thicken his feeds and keep him sitting upright as much as possible. He was also given atropine because of the severity of the repeated episodes of bradycardia, and phenobarbitone because of the possibility of epilepsy.

He was readmitted to hospital at the age of 5 months with identical symptoms that were often associated with meals or pain (for example, venepuncture). The hyperactive vagal reflexes and oesophagitis were still present. Gastro-oesophageal reflux was seen on barium meal examination. Monitoring of the oesophageal pH, however, showed that it was less than 5 during only about a third of the first hour after feeding, and this was interpreted as being within normal limits. Twenty four hour polygraphy showed minor seizures, the first one occurring while he was drinking milk (figs 1, 2, and 3). All six seizures were identical (table). Electroencephalographic discharges started in the left occipital area and then became generalised. Electroencephalography between the seizures showed either localised spike waves in the left occipital area, or generalised spike wave patterns. Thereafter he developed severe epilepsy with generalised tonic-clonic seizures.

At the age of 2½ years the neurological examination was normal, as was his development assessed by the Denver developmental screening test and the Brunet-Lezine test.

Discussion

Gastro-oesophageal reflux is common in infants of less than 15 months old[1] and may cause both oesophagitis and apnoea.[2] The most prominent feature in our case was the early onset of epilepsy with symptoms associated with gastro-oesophageal reflux and apnoea. This syndrome has not been widely described. In six of 59 infants at high risk of the sudden infant death syndrome (SIDS), Jeffery *et al*[3] reported seizures associated with gastro-oesophageal reflux diagnosed by barium meal examination and monitoring of oesophageal pH. They suggested that reflux could be a part of the autonomic dysfunction that accompanies temporal lobe seizures; this could be compared with 'eating

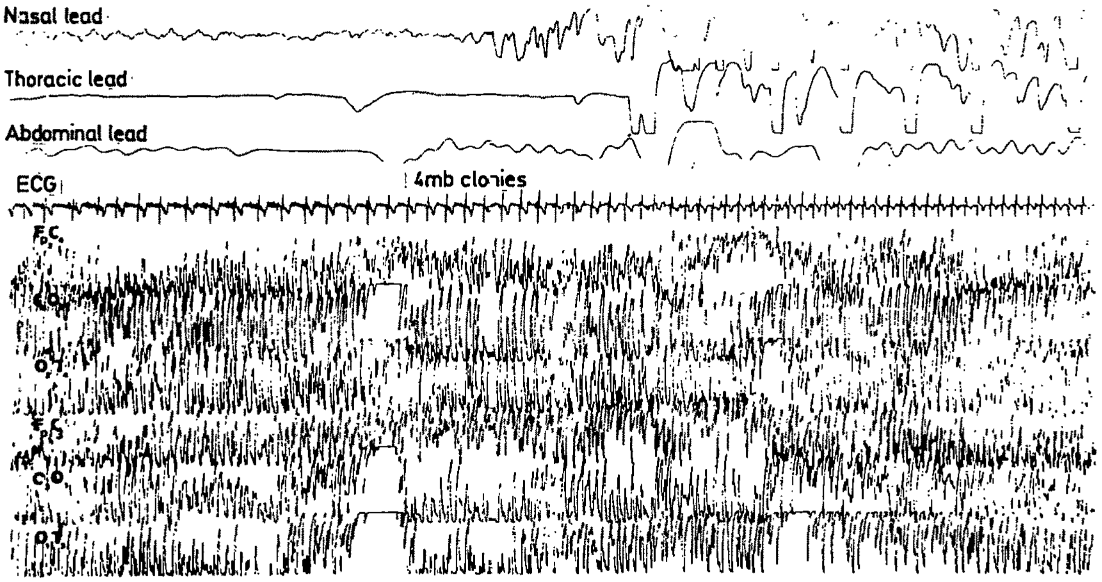


Fig 2 *The same seizure continued. The whole period of respiratory obstruction lasted 37 seconds. The term '4 mb clonies'=clonic jerks of the four limbs.*

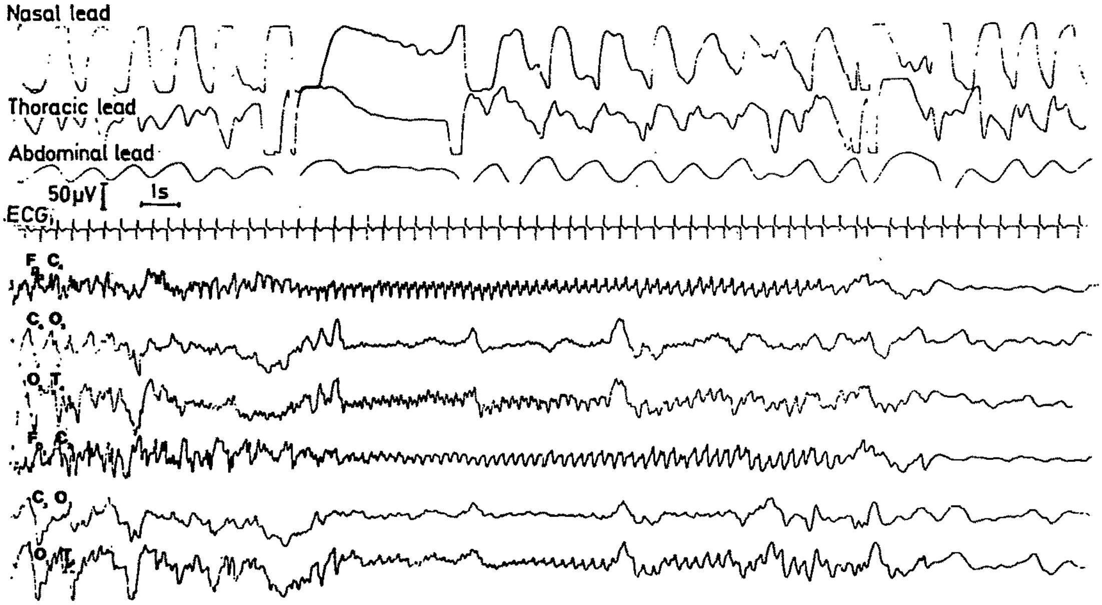


Fig 3 *The end of the same seizure. There was a short (5 s) central respiratory pause without bradycardia or clinical symptoms.*

Table *Summary of the main features of the six recorded seizures*

Electroencephalographic discharge:	Alpha-like left occipital onset Generalisation in 2–3 s Prolonged slowing after the seizure
Bradycardia:	Heart rate 60/minute 7–13 s delay after onset of discharge
Prolonged central apnoea:	Same delay as bradycardia 30–40 s duration
Duration of seizure:	30–60 s
Clinical signs:	Initial hypertonia Intense cyanosis Respiratory obstruction Ocular revulsion Few clonic movements of the limbs

epilepsy',[4] in which apparently spontaneous attacks are triggered by meals. Monod *et al*[5] reported a case similar to ours; antral dyskinesia was treated with antireflux drugs but symptoms recurred and seizures were diagnosed. After starting antiepileptic drugs the patient remained free of symptoms.

Our patient had repeated life threatening episodes of prolonged apnoea and bradycardia, and this led us to wonder if there was an association between this syndrome and SIDS. Beal[6] reported six families in which a sibling developed severe atypical or fatal seizures at the same age as a child had died of SIDS.

When a child presents with atypical repeated episodes of apnoea, repeated electroencephalography and polygraphy with stimulation may lead to the diagnosis of epilepsy and appropriate treatment can be started.

References

[1] Vandenplas Y, Sacre-Smits L. Continuous 24 hours esophageal pH monitoring in 285 asymptomatic infants 0–15 months old. *J Pediatr Gastroenterol Nutr* 1987;**6**:220–4.

[2] Shepherd RW, Wren J, Evans S, Lander M, Ong TH. Gastroesophageal reflux in children: clinical profile, course and outcome with active therapy in 126 cases. *Clin Pediatr* 1987;**26**: 55–60.

[3] Jeffery HE, Ramilly P, Read DJC. Multiples causes of asphyxia in infants at high risk for sudden infant death. *Arch Dis Child* 1983;**58**:92–100.

[4] Loiseau P, Guyot M, Loiseau H, Rougier A, Desbordes P. Eating seizures. *Epilepsia* 1986;**27**:161–3.

[5] Monod N, Peirano P, Plouin P, Sternberg B, Bouille C. Seizure-induced apnea. *Ann NY Acad Sci* 1988;**533**:411–20.

[6] Beal SM. Some epidemiological factors about sudden infant death syndrome (SIDS) in South Australia. In: Tildon JJ, Roeder LM, Steinschneider A, eds. *Sudden infant death syndrome.* New York: Academic Press, 1986:15–28.

Correspondence to Dr Y Navelet, Service d'Explorations Fonctionnelles du Système Nerveux, CH de Bicêtre, 78 rue du Général Leclerc, 94275 Kremlin Bicêtre Cedex, France.

Accepted 18 July 1988

Archives of Disease in Childhood, 1989, **64,** 360–363

Antineutrophil cytoplasm antibodies in Kawasaki disease

C O S SAVAGE,* J TIZARD,† D JAYNE,* C M LOCKWOOD,* AND M J DILLON†

**Hammersmith Hospital, and the †Hospital for Sick Children, Great Ormond Street, London*

SUMMARY Autoantibodies against components of neutrophil cytoplasm develop during adult vasculitic diseases such as Wegener's granulomatosis and microscopic polyarteritis, and they are predominantly of the IgG class. Similar but distinct antibodies have been described in children with Kawasaki disease and both IgM and IgG class antibodies are represented. This adds another clinically distinct childhood form of vasculitis to the adult forms in which autoantibodies to neutrophil cytoplasmic antigens have been detected.

Kawasaki syndrome is an acute febrile vasculitic illness of childhood which may be associated with the development of coronary artery aneurysms in 30% of cases.[1 2] The aetiology and pathogenesis are unknown, although retroviral infections[3] and immune mechanisms of tissue injury may be implicated. Both T cell and B cell abnormalities have been described by Leung *et al* including increased numbers of activated T4+ and Ia+ helper cells, reduced T8+ cells, and increased numbers of circulating B cells that spontaneously secrete IgG and IgM.[4 5] More recently they have described IgG and IgM antiendothelial cell cytotoxic autoantibodies that seem to be directed towards monokine inducible determinants on the endothelial cell surface.[6 7]

Autoantibodies have recently been described in adult vasculitic diseases including Wegener's granulomatosis and microscopic polyarteritis.[8 9] We have developed a solid phase radioimmunoassay and indirect immunofluorescence assay that detect autoantibodies to neutrophil cytoplasm components with high sensitivity and specificity in patients with Wegener's granulomatosis and microscopic polyarteritis.[10] Using these assays we screened 78 coded serum samples from 31 children, both normal control subjects and children with various illnesses (pneumonia, diabetes mellitus, IgA nephropathy, antiglomerular basement membrane antibody mediated nephritis, haemolytic uraemic syndrome, cutaneous vasculitis, Henoch-Schönlein purpura, Kawasaki disease, and microscopic polyarteritis). Serum samples from three children with Kawasaki disease contained antibodies with antineutrophil reactivity, as did four from five children with polyarteritis. This finding was therefore examined in more detail using a larger number of children with Kawasaki disease from whom serum was available.

Patients and methods

Twelve children with Kawasaki disease were investigated, 11 with the acute disease (five of these also provided serum samples when they were convalescent, from two to 12 months after the acute illness). In one patient only serum taken during the convalescent period was tested. Serial samples were available from three patients during the first month, all of whom had been treated with human immunoglobulin (Sandoglobulin). All patients fulfilled the criteria for the diagnosis of Kawasaki disease with fever and at least four of five primary features (conjunctivitis, redness of the lips or oropharynx, desquamation of the skin of the extremities, cervical lymphadenopathy, or a polymorphous rash on the trunk).[11] Clinical details are shown in the table. Control samples were taken from eight children with vasculitis that was not Kawasaki disease, Wegener's granulomatosis, or polyarteritis and from six children with other febrile illnesses.

INDIRECT IMMUNOFLUORESCENCE FOR ANTINEUTROPHIL CYTOPLASM ANTIBODIES

Autoantibodies directed towards components of normal neutrophils were sought using alcohol fixed cells, as previously described.[9] Antibody binding was detected using a fluorescein isothiocyanate rabbit antihuman IgG light chain antibody that also recognises IgM and IgA classes (Dako).

Table *Clinical details of 12 patients with Kawasaki disease*

Case No	*Age (months)*	*Sex*	*No of primary diagnostic features*	*Coronary aneurysms present*	*Platelets ($\times 10^9$/l)*	*IgG (% normal)*
1	33	Male	5	Not known	620	47
2	27	Female	5	No	653	136
3	27	Female	4	No	804	96
4	57	Male	5	Yes	1100	70
5	26	Male	5	No	598	66
6	64	Female	4	No	418	124
7	42	Female	4	Yes	861	Not known
8	13	Female	4	Yes	1340	Not known
9	12	Male	5	No	794	Not known
10	12	Female	5	Yes	1124	Not known
11	24	Female	4	Yes	790	212
12	39	Male	5	No	957	98

RADIOIMMUNOASSAYS FOR ANTINEUTROPHIL CYTOPLASM ANTIBODIES

IgG class antineutrophil cytoplasm antibodies were measured using a solid phase radioimmunoassay with a specific inhibition step, as previously described.[10] IgM class antineutrophil cytoplasm antibodies were detected using a modification of the IgG assay whereby the specific antibody binding to the solid phase ligand was detected using a 1:200 dilution of rabbit antihuman IgM in phosphate buffered saline incubated at 37°C for one hour. After washing the plate three times with phosphate buffered saline, ^{125}I labelled goat antirabbit IgG was applied as the final layer in the manner described for IgG class antibodies.

MEASUREMENT OF IgG CONCENTRATIONS AND OTHER AUTOANTIBODIES

IgG concentrations in the serum samples from patients with Kawasaki disease were measured using a standard Mancini technique.[12] Antinuclear antibodies were sought using indirect immunofluorescence techniques on HEp2 cells and using rat or monkey tissue for antigastric parietal cell antibodies, antimitochondrial antibodies, antireticulin antibodies, antiskeletal muscle antibodies, and antismooth muscle antibodies.[13]

ADSORPTION STUDIES AND BINDING TO HL60 CELLS

In adsorption studies, all serum samples were diluted to 1:8 in phosphate buffered saline, and 100 µl of diluted serum was incubated for one hour at room temperature with 10^5 fresh normal neutrophils or lymphocytes isolated with Ficoll Hypaque. After centrifugation at 120 g for five minutes, serum was aspirated off the cells and then binding by indirect immunofluorescence was compared with preadsorption serum.

Serum samples from patients with Kawasaki disease were also tested by indirect immunofluorescence for binding to cultured HL60 cells, a human promyelocyte cell line.

Results

INDIRECT IMMUNOFLUORESCENCE STUDIES

By indirect immunofluorescence, 10 of the 11 serum samples from patients with Kawasaki disease and none of those from control subjects showed binding to the cytoplasm of immobilised normal human neutrophils. Fig 1 shows the binding of antibodies in serum from patients with Kawasaki disease compared with the binding of antibodies in serum from an adult with Wegener's granulomatosis. Differences in the binding pattern between serum sample from patients with these two diseases were observed: in Kawasaki disease the cytoplasmic immunofluorescence is diffuse with linear accentuations, while in Wegener's granulomatosis the pattern is coarsely granular. Cytoplasmic staining was readily detected with all samples from patients with Kawasaki disease, although the binding pattern was most easily seen in samples that had high titres of antibody.

Preadsorption with normal polymorphonuclear leucocytes almost completely eliminated fluorescence activity compared with a minimal reduction using equal numbers of normal peripheral blood lymphocytes. Studies using HL60 cells showed that antibodies present in the serum of patients with Kawasaki disease recognised cytoplasmic determinants, although the pattern of binding was different from that seen with antibodies in Wegener's granulomatosis and microscopic polyarteritis.

RADIOIMMUNOASSAY STUDIES

Results of the radioimmunoassays are shown in fig 2. Raised titres of specific IgG or IgM antineutrophil

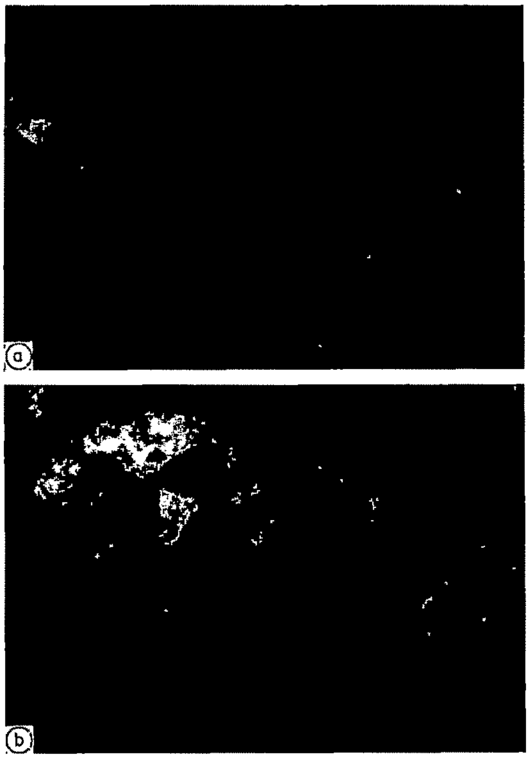


Fig 1 *Antineutrophil cytoplasm antibody staining detected by indirect immunofluorescence in a patient with (a) Kawasaki disease and (b) Wegener's granulomatosis.*

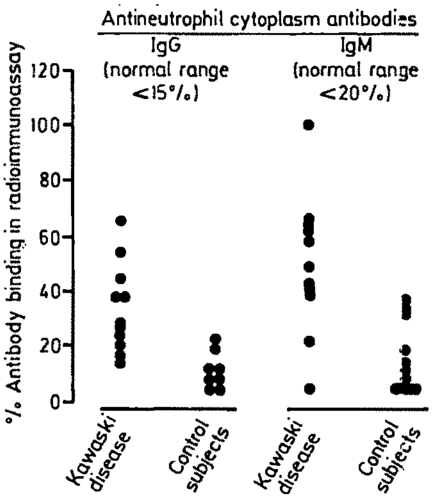


Fig 2 *Titres of IgG and IgM antineutrophil cytoplasm antibodies in serum samples from 11 patients with acute Kawasaki disease and 14 control subects.*

cytoplasm antibodies were found in serum samples from 10 of the 11 patients with acute Kawasaki disease, but not in any of the samples taken when the patients were convalescent, nor in those from the control subjects. Some samples from the control subjects showed increased binding (two in the IgG assay and three in the IgM assay) but this was found to be non-specific.

Sequential studies of IgG class antibodies in three patients from whom serum samples were available showed disappearance of the antibodies by the third and 10th days after the start of treatment with human normal immunoglobulin in two patients; in the third patient, antibody titres could still be measured after one month, despite similar treatment.

IgG CONCENTRATIONS AND OTHER AUTOANTIBODY STUDIES

The total IgG antibody concentrations ranged from 47 to 212% normal human serum (table). Antibodies to nuclear protein, mitochondria, gastric parietal cell, reticulin, and skeletal muscle were not detected. Low titres of antismooth muscle antibodies were found in seven patients 1/20 (n=2), 1/40 (n=4), and 1/80 (n=1).

Discussion

Adult vasculitic diseases such as Wegener's granulomatosis and microscopic polyarteritis are associated with autoantibodies against determinants in neutrophil cytoplasm that we have suggested are associated with the enzyme alkaline phosphatase.[9] Routine detection of these antibodies has proved useful for diagnosis.[10] Both our experience and that of other workers, therefore, suggest that these antibodies are highly specific to particular forms of vasculitis, particularly Wegener's granulomatosis and microscopic polyarteritis. We have screened more than 3000 samples over the last 2½ years and others have screened similar large numbers of patients.[8 14 15] There have been occasional reports of antineutrophil cytoplasm antibodies associated with the Churg-Strauss syndrome.[16] We have failed to detect them in Henoch-Schönlein purpura[17] although others have detected antibodies of the IgA class in a single patient with this disease.[18] We have, however, detected them in children with rapidly progressive glomerulonephritis both idiopathic (that we regard as a limited form of microscopic polyarteritis) and associated with Wegener's granulomatosis.[19] In addition, antibodies against neutrophil cytoplasm components have now been detected in acute Kawasaki disease, although they may not necessarily be directed against the same determinants as the antineutrophil cytoplasm antibodies that are present in, for example, Wegener's granulomatosis or microscopic polyarteritis.

The pathogenetic role of antineutrophil cytoplasm antibodies in the development of vasculitis remains to be established. In other studies a mouse monoclonal antibody (W8), was raised to neutrophil cytoplasm antigen[9]; subsequently it was also found to recognise determinants on vascular endothelial cells, suggesting that such cross reactivity might initiate the development of vasculitis in patients with autoantibodies to neutrophil cytoplasm antigen (unpublished observations). Antiendothelial cell antibodies have been described in Kawasaki disease. Initially IgM class antibodies to interferon gamma inducible antigenic determinants were found, and then both IgM and IgG class antibodies to tumour necrosis factor and interleukin 1 inducible endothelial cell antigens were described that differed from those induced by interferon gamma. Both varieties are cytotoxic to endothelial cells in culture. We have now found that serum from patients with acute Kawasaki disease also contains IgM and IgG antineutrophil cytoplasm antibodies that can be detected using conventional indirect immunoflourescence and radioimmunoassay techniques. Adsorption studies suggested that the antigenic determinants were peculiar to neutrophils rather than lymphocytes, and binding did not seem to be mediated through the crystallisable fragment of immunoglobulin receptors, because binding was observed with HL60 cells that either lack or have reduced expression of such receptors.[20] The target of antineutrophil cytoplasm antibodies in Kawasaki disease is unknown, and may differ from the target of antibodies in adult vasculitic disease, particularly as differences in the pattern of antibody binding to neutrophils are discernible. These antibodies may develop as part of a polyclonal activation of B cells that occurs in Kawasaki disease, such that autoantibodies develop that are directed towards both monokine inducible endothelial cell determinants and normal neutrophil cytoplasm components, as well as to smooth muscle and to antigenic components of the Hanganutziu-Deicher heterophile system where antibodies are of IgM and IgE class.[21]

The inter-relations and implications of these findings require further study but it is likely that these antibodies develop in association with immune activation that leads to vascular injury.

References

[1] Kawasaki T. MCLS: clinical observation of 50 cases. *Japanese Journal of Allergology* 1967;**16**:178–222.

[2] Yanagihara R, Todd JK. Acute febrile mucocutaneous lymph node syndrome. *Am J Dis Child* 1980;**134**:603–14.

[3] Shulman ST, Rowley AH. Does Kawasaki disease have a retroviral aetiology? *Lancet* 1986;**ii**:545–6.

[4] Leung DYM, Siegel RL, Grady S, *et al.* Immunoregulatory abnormalities in mucocutaneous lymph node syndrome. *Clin Immunol Immunopathol* 1982;**23**:100–12.

[5] Leung DYM, Chu ET, Wood N, Grady S, Meade R, Geha RS. Immunoregulatory T cell abnormalities in mucocutaneous lymph node syndrome. *J Immunol* 1983;**130**:2002–4.

[6] Leung DYM, Collins T, Lapierre LA, Geha RS, Pober JS. Immunoglobulin M antibodies present in the acute phase of Kawasaki syndrome lyse cultured vascular endothelial cells stimulated by gamma interferon. *J Clin Invest* 1986;**77**:1428–35.

[7] Leung DYM, Geha RS, Newburger JW, *et al.* Two monokines, interleukin 1 and tumour necrosis factor, render cultured vascular endothelial cells susceptible to lysis by antibodies circulating during Kawasaki syndrome. *J Exp Med* 1986;**164**:1958–72.

[8] van der Woude FJ, Rasmussen N, Lobatto S, *et al.* Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. *Lancet* 1985;**i**:425–9.

[9] Lockwood CM, Bakes D, Jones S, Whitaker KB, Moss DW, Savage COS. Association of alkaline phosphatase with an autoantigen recognized by circulating anti-neutrophil antibodies in systemic vasculitis. *Lancet* 1987;**i**:716–20.

[10] Savage COS, Winearls CG, Jones SJ, Marshall PD, Lockwood CM. Prospective study of radioimmunoassay for antibodies against neutrophil cytoplasm in diagnosis of systemic vasculitis. *Lancet* 1987;**ii**:1389–93.

[11] Centers for Disease Control. Kawasaki disease—New York. *MMWR* 1980;**29**:61–3.

[12] Ingild A. Single radial immunodiffusion. *Scand J Immunol* 1984;**18**(suppl 10):41–56.

[13] Humbel R, Kadusch P. Use of Hep-2 cells in the IF test for detection of anti-nuclear antibodies. *Protides of the Biological Fluids* 1985;**33**:385.

[14] Hall JB, Wadham McN, Wood CJ, Ashton V, Adam WR. Vasculitis and glomerulonephritis: a sub-group with an anti-neutrophil cytoplasm antibody. *Aust NZ J Med* 1984;**14**:277–8.

[15] Ludemann G, Gross WL. Autoantibodies against cytoplasmic structures of neutrophil granulocytes in Wegener's granulomatosis. *Clin Exp Immunol* 1987;**69**:350–7.

[16] Wathen CW, Harrison DJ. Circulating anti-neutrophil antibodies in systemic vasculitis. *Lancet* 1987;**i**:1037.

[17] Knight JF, Harada T, Thomas MAB, *et al.* IgA rheumatoid factor and other autoantibodies in acute Henoch-Schönlein purpura. *Contrib Nephrol* 1988 (in press).

[18] Van der Wall Bake AWL, Lobatto S, Jonges L, Daha MR, van Es LA. IgA antibodies directed against cytoplasmic antigens of polymorphonuclear leukocytes in patients with Henoch-Schönlein purpura. *Adv Exp Med Biol* 1987;**216B**:1593–8.

[19] Walters MDS, Savage COS, Dillon MJ, Lockwood CM, Barratt TM. Anti-neutrophil cytoplasm antibodies in children with crescentic glomerulonephritis. *Arch Dis Child* 1988;**63**:814–7.

[20] Koeffler HP. Induction of differentiation of human acute myelogenous leukemia cells: therapeutic implications. *Blood* 1983;**62**:709–21.

[21] Takiguchi M, Tamura T, Goto M, Kusakawa S, Milgram F, Kano K. Immunological studies on Kawasaki disease. I. Appearance of Hanganutziu-Deicher antibodies. *Clin Exp Immunol* 1984;**56**:345–52.

Correspondence to Dr C O S Savage, Renal Unit, Royal Postgraduate Medical School, Du Cane Road, London W12 0NN.

Accepted 12 September 1988

Archives of Disease in Childhood, 1989, 64, 364–368

Oesophageal atresia and associated anomalies

S CHITTMITTRAPAP, L SPITZ, E M KIELY, AND R J BRERETON

The Hospital for Sick Children, Great Ormond Street, London

SUMMARY Of 253 infants with oesophageal atresia treated over an eight year period, 122 (48%) had a total of 213 other anomalies. Most commonly affected were the cardiovascular (61 cases, 29%), anorectal (30 cases, 14%), and genitourinary (29 cases, 14%) systems. The VATER (or VACTERL) association was present in 10% of cases, but occurred more often in patients who had oesophageal atresia without an associated tracheo-oesophageal fistula (3/13, 23%). The level of the associated anorectal malformation was not associated with the type of oesophageal atresia. The presence and severity of other anomalies did not influence the basic approach to treatment of the oesophageal atresia—that is, primary repair whenever possible. Despite aggressive treatment, cardiac malformations were the most common cause of death. There were five infants with the CHARGE association, two with Potter's syndrome, and two with 'SCHISIS' syndrome (cleft lip and palate, omphalocoele, and hypogenitalism).

In infants with oesophageal atresia with or without tracheo-oesophageal fistula, the incidence of associated congenital abnormalities ranges from between 40–57% of patients.[1-6] The well known occurrence of three or more of these anomalies, Vertebral defects, Anorectal malformation, TracheoEsophageal fistula, Renal anomaly and Radial dysplasia, is not uncommon and has been amalgamated to form the 'VATER' association,[7] later expanded to 'VACTERL' when Cardiac and Limb defects were added.[8 9]

The early diagnosis of these other anomalies is important, not only so that the correct operative approach may be planned but also so that the prognosis for the infant may be assessed, because the mortality and morbidity among infants with oesophageal atresia is directly related to the nature and severity of the other malformations.

Patients and methods

The records of 253 patients with oesophageal atresia with or without tracheo-oesophageal fistulas treated between January 1980 and December 1987 were retrospectively reviewed. The presence and variety of other anomalies were noted. A comprehensive analysis of these anomalies was carried out and correlated with the type of oesophageal atresia, its management, and the results of treatment. Overall mortality included both early and late deaths.

Results

Of 253 patients with oesophageal atresia, 122 (48%) had a total of 213 other anomalies. The cardiovascular system was the most commonly affected (61 cases, 29%). The second most common group was anorectal malformations (30 cases, 14%). The complete range of anomalies is listed in table 1. The highest incidence (13 of 20, 65%) was in infants who had oesophageal atresia without tracheo-oesophageal fistula, of whom three had the VATER association. Of 210 infants with oesophageal atresia accompanied by tracheo-oesophageal fistulas, 104 (50%) had other anomalies, while only one of 10 patients (10%) with H type tracheo-oesophageal fistulas had other anomalies. Several syndromes have

Table 1 *Details of anomalies according to organ system affected*

System affected	*No (%) of anomalies*
Cardiovascular	61 (29)
Anorectum	30 (14)
Genitourinary	29 (14)
Gastrointestinal (excluding anorectum)	27 (13)
Vertebral and skeletal	21 (10)
Respiratory	13 (6)
Genetic	8 (4)
Other	24 (11)
Total	213 (100)

been identified as being associated with oesophageal atresia (table 2).

Five infants had multiple anomalies that fulfilled the criteria for the CHARGE association (Coloboma, **H**eart disease, **A**tresia choanae, **R**etarded growth and development, **G**enital hypoplasia, and **E**ar anomalies or deafness).[10] Four of them had the common variety of atresia with a distal fistula, and one had oesophageal atresia with proximal and distal fistulas. Two patients had Potter's syndrome (renal agenesis, pulmonary hypoplasia, and dysmorphism with typical facies), two had omphalocoele, cleft lip, cleft palate, and genital hypoplasia, which together constitute the 'SCHISIS' association.[11]

The VACTERL association was present in 25 patients (10% of 253 cases), of whom 18 were boys and seven were girls. Their gestational ages ranged from 29 to 40 weeks (mean 35) and birth weights from 1160 to 3035 g (mean 2430). The frequency of the various components of VATER or VACTERL association are shown in table 3.

The other anomalies were the most common causes of mortality in patients with oesophageal atresia with or without tracheo-oesophageal fistulas. Twenty (32·8%) of the 61 infants with cardiac anomalies died (table 4). Five infants with complex lesions died before undergoing any surgery and 10 died after cardiac operations. It is noteworthy that patients with multiple other anomalies had more complex cardiovascular malformations, which have a higher mortality than the simpler cardiac defects that occur as isolated other anomalies. The latter consisted mainly of ventricular septal defects or persistent patent ductus arteriosus and had a good prognosis.

Table 3 *Association of combinations of VACTERL defects and tracheo-oesophageal anomalies*

Main VACTERL defects	*No (%) of cases*	
Vertebral anomalies	9 (36)	
Anorectal malformations:	18 (72)	
High anomalies		9
Intermediate anomaly		1
Low anomalies		5
Cloacal anomalies		3
Tracheo-oesophageal anomalies:	25 (100)	
Oesophageal atresia with distal tracheo-oesophageal fistula		21
Oesophageal atresia with both proximal and distal tracheo-oesophageal fistula		1
Oesophageal atresia with no tracheo-oesophageal fistula		3
Renal anomalies	14 (56)	
Radial dysplasia or aplasia	3 (12)	
Cardiac anomalies	20 (80)	
Limb defects	7 (28)	
Other defects present in VACTERL patients:	13 (52)	
Duodenal atresia		2
Malrotation of the intestine		2
Single umbilical artery		2
Omphalocoele		1
Pyloric atresia		1
Ileal atresia		1
Absent right upper lobe of lung		1
Polysplenia		1
Hypospadias		1
High arch palate and mental retardation		1

Table 2 *Association between complex anomalies and specific syndromes*

Type of oesophageal atresia[22]	*VATER or VACTERL*	*CHARGE*	*Potter's syndrome*	*'SCHISIS' syndrome*	*Trisomy 18*	*One or two systems affected*	*>Two systems affected*	*Total No*	*% Affected cases according to type of oesophageal atresia*
Oesophageal atresia with distal tracheo-oesophageal fistula (type C)	21*	4	2*	2	2	61	13	104	50
Oesophageal atresia with proximal tracheo-oesophageal fistula (type B)	0	0	0	0	0	1	0	1	20
Oesophageal atresia with both proximal and distal tracheo-oesophageal fistula (type D)	1†	1†	0	0	0	2	0	3	43
Isolated oesophageal atresia (type A)	3	0	0	0	0	9	1	13	65
H type tracheo-oesophageal fistula with no oesophageal atresia (type E)	0	0	0	0	0	0	1	1	10
Total	25*†	5†	2*			73	15	122	

*†One patient had both complex anomalies.

Table 4 *Mortality in patients with cardiovascular anomalies*

Cardiovascular defects	*No of patients*	*No of deaths*
Ventricular septal defect	10	-
Patent ductus arteriosus	7	-
Tetralogy of Fallot	7	2
Ventricular septal defect, patent ductus arteriosus, and pulmonary stenosis	5	-
Ventricular septal defect and patent ductus arteriosus	4	-
Atrial septal defect, patent ductus arteriosus, pulmonary stenosis, and atrioventricular canal	4	3
Atrial septal defect	3	0
Pulmonary stenosis	3	0
Total anomalous venous drainage	2	2
Ventricular septal defect, double outlet right ventricle, and patent ductus arteriosus	2	-
Ventricular septal defect, patent ductus arteriosus, and atrial septal defect	2	-
Patent ductus arteriosus, aortopulmonary window, and aortic stenosis	2	0
Transposition of great vessels	1	-
Single ventricle, patent ductus arteriosus, and pulmonary stenosis	1	0
Hypoplastic heart	1	-
Isolated right sided aortic arch	4	0
Right sided aortic arch and tetralogy of Fallot	1*	-
Right sided aortic arch, patent ductus arteriosus, ventricular septal defect, and pulmonary stenosis	2*	0
Isolated coarctation of the aorta	1	-
Coarctation of the aorta and atrial septal defect	1	-
Coarctation of the aorta and ventricular septal defect	1	-
Double aortic arch	2	-
Total	61	20 (33%)

*Dextrocardia.

Thirty patients had anorectal malformations (14% of total cases). Six of 20 (30%) of the infants who had oesophageal atresia without tracheo-oesophageal fistulas were affected compared with 23 of 210 (11%) infants with the more common type of oesophageal atresia and distal tracheo-oesophageal fistulas (table 5). The incidence of the various types of anorectal malformations and the types of oesophageal atresia are also shown in table 5.

TREATMENT

Of the 122 patients with oesophageal atresia and other anomalies, no operation was carried out in eight patients because of the complexity of the cardiac malformations or specific syndromes (for example, Potter's or trisomy 18) that were incompatible with survival. Eight infants underwent preliminary gastrostomies and primary repair was delayed in five patients so that their conditions could be stabilised preoperatively. Cardiac anomalies were managed aggressively by either medical or surgical means. The remaining patients (101, 83%) underwent primary extrapleural repair of the oesophageal defect. The overall survival rate in the 122 patients was 70%.

Discussion

A total of 122 (48%) of the infants with oesophageal atresia had other congenital anomalies, an incidence that confirms other large reported series.[1-6] Early failure of midline mesodermal organogenesis resulting in the simultaneous occurrence of multiple defects in various organs has been suggested as an explanation of this phenomenon.[7 8 12]

Table 5 *Association between types of anorectal malformation and types of oesophageal atresia*

Type of oesophageal atresia[22]	*Type of anorectal malformation*				*Total No*	*% Anorectal malformations with each type of oesophageal atresia*
	High	*Intermediate*	*Low*	*Cloacal*		
Oesophageal atresia with distal tracheo-oesophageal fistula (type C)	11	0	10	2	23	11
Oesophageal atresia with proximal tracheo-oesophageal fistula (type B)	0	0	0	0	0	0
Oesophageal atresia with both proximal and distal tracheo-oesophageal fistula (type D)	1	0	0	0	1	14
Isolated oesophageal atresia (type A)	2	1	2	1	6	30
H type tracheo-oesophageal fistula with no oesophageal atresia (type E)	0	0	0	0	0	0
Total No (%)	14 (47)	1 (3)	12 (40)	3 (10)	30 (100)	

The VATER or VACTERL association is the most widely known variety of multiple mesodermal defects. The tracheo-oesophageal component is present in 20–67% of patients with the VATER association,[13 14] and 5–17% of infants with oesophageal atresia fulfill the criteria for the association.[5 13 15] Other mesodermal defects apart from the VACTERL association may occur and may be collectively referred to as 'axial mesodermal dysplasia'.[16] The anomalies associated with oesophageal atresia include trisomy 21,[5 17] trisomy 18 (two cases in this series),[7] Potter's syndrome (two cases in this series),[14] Goldenhar's syndrome,[7] and duodenal atresia.[5 18]

Khoury *et al*[13] used a birth defects surveillance registry of 11 366 cases to document the incidence of the six suggested combinations of VATER defects. An increased incidence of certain specific defects occurred in 76 patients with VATER—for example, oral clefts (n=9), omphalocoeles (n=3) and diaphragmatic hernias. They therefore questioned whether the VATER or VACTERL association was one example of a wider range of multiple anomalies. In the series of Weaver *et al*[14] of 46 infants with VATER, five had cleft lips or palates. In our series of patients with oesophageal atresia, six had cleft lips or palates and one had an omphalocoele. There were also two other cases that could conform with the 'SCHISIS' association (two or more anomalies including either the neural tube defect, or oral cleft, or omphalocoele, or diaphragmatic hernia) a previously unrecognised association.[11]

Pagon *et al*[10] and Valente and Brereton[19] reported series of patients with oesophageal atresia and the CHARGE association. Weaver *et al*[14] documented two patients with both CHARGE and VATER associations and suggested an association between the two. In our series of infants with oesophageal atresia, five had the CHARGE association, but only one had features of the VATER association.

Infants with oesophageal atresia and other anomalies can be clearly divided into two groups. The first group comprises infants with severe anomalies generally incompatible with survival—for example, trisomy 18, Potter's syndrome, and tracheal agenesis. In our series there were 10 such infants and they all died. In the second group of 112 infants mortality is directly related to the severity of the associated anomalies. Cardiac defects were the most common cause of death and despite aggressive management mortality was high (33%). Greenwood and Rosenthal[20] reported a 79% mortality in 48 infants with associated cardiovascular lesions in a series of 278 infants with oesophageal atresia. Piekarski and Stephens[15] reported an increased mortality in infants with oesophageal atresia and anorectal malformations—30% with one anomaly and 50% with combined lesions. Even though serious anomalies placed the infants into a higher risk group according to the criteria of Waterson *et al*[21] primary repair was considered wherever possible.

Prompt recognition of any associated anomalies in patients with oesophageal atresia with or without tracheo-oesophageal fistulas is important, especially cardiovascular defects as these should be treated aggressively. Most of these infants are good candidates for surgical correction and the aim of treatment should be total correction of the various anomalies rather than palliative procedures.

References

[1] Waterston DJ, Cater REB, Aberdeen E. Oesophageal atresia and tracheoesophageal fistula. A study of survival in 218 infants. *Lancet* 1962;i:819–22.

[2] German JC, Mahour HG, Woolley MM. Esophageal atresia and associated anomalies. *J Pediatr Surg* 1976;**11**:299–306.

[3] Holder TM. Esophageal atresia and tracheoesophageal fistula. In: Ashcraft KW, Holder TM, eds. *Pediatric esophageal surgery*. Orlando: Grune and Stratton, 1986:29–52.

[4] Spitz L, Kiely E, Brereton RJ. Esophageal atresia: five year experience with 148 cases. *J Pediatr Surg* 1987;**22**:103–8.

[5] Barry JE, Auldist AW. The VATER association—one end of a spectrum of anomalies. *Am J Dis Child* 1974;**128**:769–71.

[6] Hicks LM, Manfield PB. Esophageal atresia and tracheoesophageal fistula: review of thirteen years' experience. *J Thorac Cardiovasc Surg* 1981;**81**:358–63.

[7] Quan L, Smith DW. The VATER association. Vertebral defects, Anal atresia, T-E fistula with esophageal atresia, Radial and Renal dysplasia: a spectrum of associated defects. *J Pediatr* 1973;**82**:104–7.

[8] Temtamy SA, Miller JD. Extending the scope of the VATER association: definition of the VATER syndrome. *J Pediatr* 1974;**85**:345–9.

[9] Nora AH, Nora JJ. A syndrome of multiple congenital anomalies associated with teratogenic exposure. *Arch Environ Health* 1975;**30**:17–21.

[10] Pagon RA, Graham JM Jr, Zonana J, Yong SL. Coloboma, congenital heart disease and choanal atresia with multiple anomalies: CHARGE association. *J Pediatr* 1981;**99**:223–7.

[11] Czeizel A. SCHISIS-association. *Am J Med Genet* 1981;**10**:25–35.

[12] Weber TR, Smith W, Grosfeld JL. Surgical experience in infants with VATER association. *J Pediatr Surg* 1980;**15**:849–53.

[13] Khoury MJ, Cordero JF, Greenberg F, Janes LM, Erickson JD. A population study of the VACTERL association: evidence for its etiologic heterogenicity. *Pediatrics* 1983;**71**:815–20.

[14] Weaver DD, Mapstone CL, Yu P. The VATER association. Analysis of 46 patients. *Am J Dis Child* 1986;**140**:225–9.

[15] Piekarski DH, Stephens FD. The association and embryogenesis of tracheoesophageal and anorectal anomalies. *Progress in Pediatric Surgery* 1976;**9**:63–76.

[16] Russel LJ, Weaver DD, Bull MJ. The axial mesodermal dysplasia spectrum. *Pediatrics* 1981;**67**:176–82.

[17] Ravinowitz JG, Moseley JE, Mitty HA, Hirschorn K. Trisomy 18, esophageal atresia, anomalies of the radius and congenital hypoplastic thrombocytopenia. *Radiology* 1967;**89**:448.

[18] Spitz L, Ali M, Brereton RJ. Combined esophageal and duodenal atresia: experience of 18 patients. *J Pediatr Surg* 1981;**16**:4–7.

[19] Valente A, Brereton RJ. Oesophageal atresia and the

CHARGE association. *Pediatric Surgery International* 1987;**2:** 93–4.

[20] Greenwood RD, Rosenthal A. Cardiovascular malformations associated with tracheoesophageal fistula and esophageal atresia. *Pediatrics* 1976;**57:**87–90.

[21] Waterson DJ, Carter REB, Aberdeen E. Congenital tracheo-oesophageal fistula in association with oesophageal atresia. *Lancet* 1963;**ii:**55–7.

[22] Gross RE. *Surgery of infancy and childhood.* Philadelphia: WB Saunders, 1953:75–102.

Correspondence to Professor L Spitz, Department of Surgery, Institute of Child Health, 30 Guilford Street, London WC1N 1EH.

Accepted 5 September 1988

Archives of Disease in Childhood, 1989, **64,** 369–372

Maternal insecurity and failure to thrive in Asian children

T R FENTON,* R BHAT,† A DAVIES,* AND R WEST*

*Departments of *Paediatrics and †Child Psychiatry, St George's Hospital Medical School, London*

SUMMARY Four Asian babies were investigated because they failed to thrive. In all four cases the failure to thrive was a result of the mother's social isolation and inability to communicate, and to the father's refusal to accept that there was a problem in the family.

Non-organic (emotional) failure to thrive is common in infancy.[1 2] The children may have a characteristic watchful posture, but often the only abnormal findings are that they are underweight for height and bone age is retarded.[3] They may also show retarded language development and social adaptive behaviour[3] Abnormal social interaction between the parents, and between the parents and their child, may also be observed during the interview.[3] The common finding is an inadequate intake of calories,[3–5] the reasons for which are complex. A small group of children simply refuse food[6] but most have obvious family problems. Social deprivation, maternal depression, and inadequate parenting skills are common contributory factors in the psychopathology in these families.[6 7]

It has been suggested that the child may contribute to the disturbed family relationships,[5] and a subgroup of children has been described[8] who from the age of 6 months actually resist the mother's attempt to feed them thereby exacerbating the mother's inability to handle the child appropriately and leading to a separation disorder. We report four Asian children who, though similar to this last group, show differences caused by cultural and social circumstances.

Case reports

CASE 1

This girl was well until she was 3 months old when weaning was attempted. She was initially breast fed, and had been changed uneventfully to formula feed when she was 2 months old. When infant foods were introduced at the age of 6 months she started vomiting and refusing solid food. Despite dietary advice her weight gain continued to be poor. When she was referred at the age of 1 year there were no abnormal physical findings apart from some wasting. All investigations including histological examination of a jejunal biopsy specimen were normal.

The family history is summarised in the table. Her mother had given birth to an anencephalic infant shortly after she arrived in England two years earlier, and the patient was conceived within a few months of this baby's death. The family accommodation was poor and cramped; the mother spoke little English and was socially isolated. Furthermore, at weaning the mother had been unable to obtain her traditional foods and had relied on strained puddings. After psychiatric treatment, the mother was able to talk about her isolation and the development of social phobia, and acknowledge the family's grief over—and need to mourn—the dead baby. With the aid of the social services transfer to more suitable accommodation was arranged. The mother gained sufficient confidence to talk about her grief, she took appropriate dietary advice, and joined English classes. This was accompanied by a marked improvement in the child's weight gain.

CASE 2

This girl breast fed normally until she was 5 months old when her mother became unsure of her milk supply and the baby refused to accept any other milk or solids. She subsequently failed to thrive but no cause for this could be found despite extensive investigation. She was the first child of the father's second marriage. The mother had been anxious about her capacity to bear children because of a miscarriage two years previously. The mother, who seemed withdrawn and depressed, was socially isolated and resentful about the lack of support she received from the father. Her anxieties, coupled with the patient's faddiness about food, led to a cycle of food refusal and comforting at the breast.

Table *Family histories*

	Case No			
	1	*2*	*3*	*4*
Country of origin of parents:	Bangladesh	Pakistan	Bangladesh	Pakistan
Father:	48	47	41	39
	Waiter	Banker	Banker	Banker
		First wife (mother's sister) died of typhoid	Divorced first wife after her mental breakdown	
	Arrived England 1962	Arrived England 1969	Arrived England 1969	Arrived England 1970
Mother:	33	32	26	22
	Housewife	Housewife (teacher)	Housewife	Housewife (teacher)
	Arrived England 1983	Arrived England 1978	Arrived England 1983	Arrived England 1981
	Depressed	Depressed	Depressed	Depressed
Mother's obstetric history:	1973 Boy 1975 Miscarriage 1976 Miscarriage 1982 Boy 1983 Girl anencephalic at 34 weeks' gestation 1985 Girl propositus	1981 Miscarriage 1983 Girl propositus	No previous pregnancies 1983 Boy propositus	No previous pregnancies 1983 Girl propositus
Social circumstances:	Live in two rooms above restaurant	Good	Good	Good

After repeated home visits by a child psychiatrist the mother eventually admitted her feelings of inadequacy as a mother, and the stress of being a second wife and stepmother.

The psychiatrist's ability to speak in the mother's native language was a great help, but was even more important in setting appropriate tasks with mother and child as part of a simple behavioural programme aimed at ensuring mother's full attention to the child at meal times and providing separate periods when the mother would take part with the child in activities other than feeding (for example, playing and story telling). This led to a gradual improvement in the relationship between mother and child and a steady but slow improvement in the child's weight gain over the course of one year.

CASE 3

This child progressed normally until the age of 5 months when, at the first attempt at weaning, he started vomiting all solids. He was investigated when he was 6 months old for failure to thrive, and no cause was found. A period of excluding cows' milk from his diet made no difference to his symptoms, and breast milk continued to be the main component of his diet until after he was 9 months old. Continuing weight loss prompted a further admission to hospital when he was 18 months old. Investigations including histological examination of a jejunal biopsy specimen were normal (apart from a mild dietary iron deficiency anaemia). With previous experience in mind, the family was referred to a child psychiatrist.

The father's first marriage had ended in divorce. The first wife had become depressed after the death of their first child at 14 months of congenital heart disease. The patient's mother, who spoke little English, had only recently arrived from Bangladesh and was socially isolated and depressed. Things were made worse by the feeling of inadequacy the mother had when she compared herself with her flamboyant westernised sister who lived nearby.

The patient ignored all food put before him and tried to make his mother play and tell stories. Psychiatric treatment concentrated on allowing his mother to explore her feelings about the stresses in the perinatal phase and the problems of being a second wife, and also understanding her own sibling rivalry with her sister. Firm dietary advice and support, including the mother making contact with other mothers at a local play group, was followed by satisfactory weight gain (figure).

CASE 4

This boy, who was born at 37 weeks' gestation and was small for gestational age, progressed well at first showing good catch up growth on bottle feeding. He started vomiting and refusing solid foods at weaning. When he was 8 months old full investigation failed to show any cause for his failure to thrive.

Like the other mothers, this patient's mother had arrived in England long after her husband and with

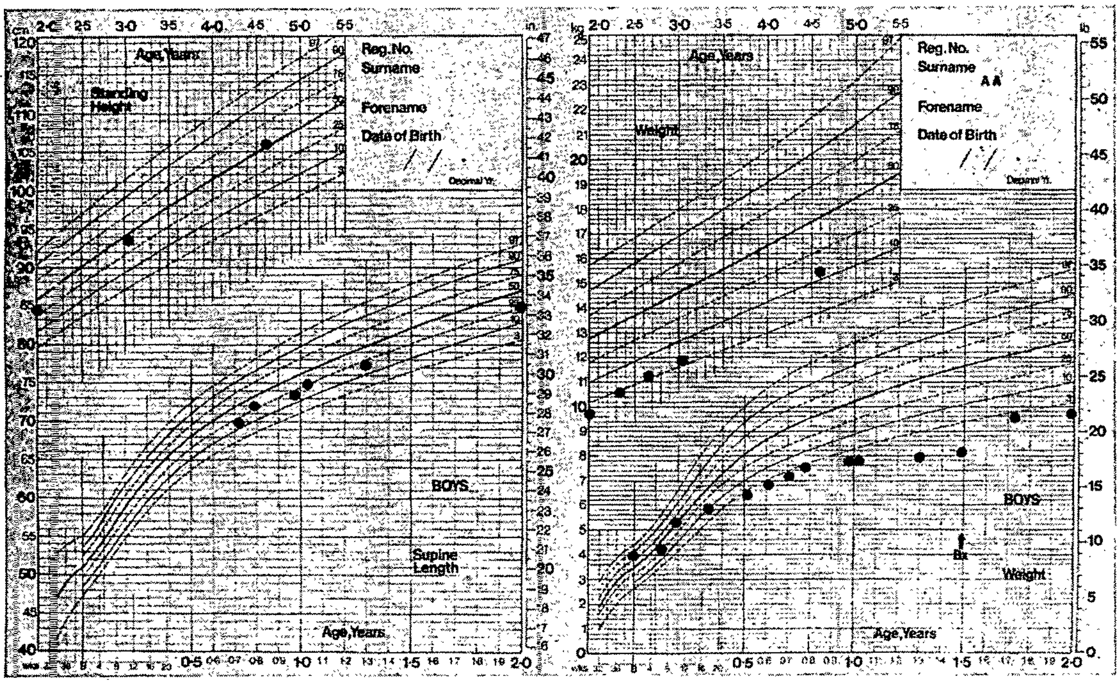


Fig 1 *Growth chart of case 3. The weight increased at the time of psychiatric treatment after admission to hospital for jejunal biopsy (Bx).*

her lack of English had become isolated and depressed (in contrast with Pakistan where she had been a teacher with a full social life). Despite this, it took several home visits by a child psychiatrist to gain the mother's confidence. The mother's inexperience and isolation had resulted in punitive attempts to force the child to eat. Introduction of a behaviour modification programme, and encouraging the mother to talk about her marital dificulties, loss of occupation, and social isolation as well as widening her social contacts by enrolling the child in a play group, resulted in relief of the mother's depression and the child gained weight.

Discussion

These four patients show several similarities. All developed pronounced failure to thrive at the time of weaning, their weights falling from on or above the third centile to well below the third centile. They continued to grow appropriately, however, being between the third and 50th centiles for height. All investigations, which included full blood count, estimation of urea and electrolyte concentrations, clotting studies, liver function tests, estimation of immunoglobulin concentrations, midstream urine culture, and examination of a jejunal biopsy specimen, were normal. All four mothers experienced difficulty with weaning, and breast milk remained the mainstay of nutrition during the first year for two patients. The lack of advice normally provided by the extended family contributed to their problems; this was further compounded by difficulties in finding suitable weaning preparations that did not contain substances that were unacceptable because of their religious beliefs (for example, non-halal meat, animal fat, and rennet that are found in such infant foods as lamb and chicken dinners, and cheese savouries). Dietary assessment showed that all had diets with adequate protein content but they were low in calories, vitamin C, and iron. All patients had low serum iron concentrations with normal iron binding capacity, and three were mildly anaemic (haemoglobin concentrations 104–108 g/l). None, however, responded to iron. Unlike many children who fail to thrive, these patients were bright and happy and developing normally, but were intensely attached to their mothers.

The mothers had all lost self confidence. They had all recently arrived in England and felt isolated and insecure. In two cases, the mother's previous child had died and in one there had been a preceding miscarriage. The mother's poor self image was further worsened by reciprocal interactions between her and the baby.[5] Improvement in the mother's social contacts (and home conditions when possible), coupled with intervention by the child psychiatrist (who permitted the mothers to discuss their marital difficulties and also provided simple behavioural treatment) resulted in weight gain by all the patients. This was made easier by the psychiatrist being able to communicate with the mothers in their native language, the importance of which in the development of psychotherapeutic relationships has previously been described.[9]

A sense of incompleteness pervades these cases, however. Others have noted that the fathers of children with emotional failure to thrive are often either absent or ineffective.[2] Fathers were present in all these families; they were all much older than their wives. Two had been married before and all had lived in England for long periods before their wives joined them. None really participated in the treatment and all denied that there were any problems at home. It is likely that these fathers contributed substantially to the mothers' insecurity, which lay at the root of the psychiatric disorders in these families.

References

[1] Hannaway PJ. Failure to thrive. A study of 100 infants and children. *Clin Pediatr* 1970;**9**:96–9.

[2] Leonard FM, Rhymes JP, Solnit AJ. Failure to thrive in infants. A family problem. *Am J Dis Child* 1966;**111**:600–12.

[3] Goldbloom RB. Failure to thrive. *Pediatr Clin North Am* 1982;**29**:151–66.

[4] Whitten CF, Pettit MG, Finschoff J. Evidence that growth failure from maternal deprivation is secondary to undereating. *JAMA* 1969;**209**:1675–82.

[5] Skuse DH. Non organic failure to thrive. A reappraisal. *Arch Dis Child* 1985;**60**:173–8.

[6] Graham P. Development and its disorders. *Child psychiatry—a developmental approach.* Oxford: Oxford University Press, 1986:54–63.

[7] Evans SL, Reinhardt JB, Succop RA. Failure to thrive. A study of 45 children and their families. *Journal of the American Academy of Child Psychiatry* 1972;**11**:440–57.

[8] Chatoor I, Egan J. Non organic failure to thrive and dwarfism due to food refusal: a separation disorder. *Journal of the American Academy of Child Psychiatry* 1983;**22**:294–301.

[9] Stern J. Language and authority in psychotherapy. *Group Analysis* 1987;**3**:221–35.

Correspondence to Dr T Fenton, Greenwich District Hospital, Vanburgh Hill, London SE10 9HE.

Accepted 18 September 1988

Archives of Disease in Childhood, 1989, **64,** 373–378

Energy and nutrient intakes in cystic fibrosis

R M BUCHDAHL, C FULLEYLOVE, J L MARCHANT, J O WARNER, AND
M J BRUETON

Paediatric Cystic Fibrosis Clinic, Brompton Hospital, London

SUMMARY The diets of 20 children with cystic fibrosis were analysed for energy and nutrient content with simultaneous measurement of energy losses in stools. Median energy intakes were in excess of the WHO estimated daily requirements (118·2%) when expressed as MJ/kg/24 hours, the excess almost accounted for by energy losses in the stools. When expressed as MJ/24 hours, however, median energy intakes were 98·7% of that estimated for normal children of median weight for age. Compared with recently published data for normal school children the fat content of the diet was reduced (30·0%) as were intakes of iron and zinc. Children whose whole milk intakes were high had the greatest amount of fat and energy in their diets and were able to absorb energy in excess of that recommended. We conclude that many children with cystic fibrosis are still on low fat diets and whole milk is the single most useful food for the provision of extra dietary fat and energy.

The traditional dietary advice given to families with children who have cystic fibrosis has been that they should be given diets low in fat in order that symptoms of steatorrhoea secondary to pancreatic disease may be alleviated.[1] In 1974, however, Crozier and his colleagues in the Toronto cystic fibrosis clinic reported that by increasing dietary fat and giving appropriate enzyme treatment, children with cystic fibrosis could benefit from the increased energy density of the diet. Early studies confirmed improved growth velocities and showed higher circulating blood cholesterol and triglyceride concentrations.[2] In the late 1970s many of their patients had weights and heights comparable with those of their normal adolescent counterparts.[3] This improvement in growth and nutritional state is associated with an increased survival, recently published figures giving a median survival of 30 years.[4]

In the United Kingdom the change to higher fat diets has been slower[5] but in the past three or four years as the more effective enteric coated microsphere enzyme preparations have become more widely available, cystic fibrosis clinics have begun to adopt this policy. During 1986 we undertook a dietary survey of a group of children with cystic fibrosis to find out how far this change had progressed and what effect it had had on the nutrient composition of their diet and absorption of energy.

Subjects and methods

Twenty three children with cystic fibrosis confirmed by sweat iontophoresis were selected at random from the cystic fibrosis clinic. These children and their families had all received previous advice on nutrition that had emphasised the importance of not restricting fat. Families were interviewed at each outpatient attendance and give a pamphlet detailing recommended foods. For the outpatient study all the children were in a clinically stable state. Clinical assessment included scoring using the Shwachman method.[6] Weight and height were measured using standard techniques and expressed as standard deviation scores (measured value−expected value for age divided by the standard deviation of expected value).[7]

Expected values and standard deviations for normal children were derived from the growth tables of Tanner and Whitehouse and of the Department of Growth and Development, Hospital for Sick Children, Great Ormond Street.[8] The study was approved by the Brompton Hospital ethical committee and informed consent was obtained from both parents and children.

Dietary and absorbed energy intakes were calculated from seven day prospective records of the weights of all food consumed and three day collections of faeces. All energy containing foods and

Table 1 *Clinical data and nutrient intake/24 hours of 20 children with cystic fibrosis*

	Case numbers								
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Age (years)	5·3	6·2	8·0	8·6	8·8	9·5	9·6	10·0	10·4
Sex (M/F)	M	F	M	M	M	M	F	F	F
Weight (kg)	18·3	16·3	21·6	35·0	20·7	27·1	28·3	23·0	23·1
Energy intake:									
MJ	7·19	5·01	6·81	11·9	6·91	7·91	9·55	7·89	6·74
per kg	0·393	0·307	0·315	0·340	0·334	0·293	0·337	0·343	0·292
Percentage energy intake:									
As % of WHO estimated average daily energy requirements:									
Median weight for age	95	70	79	137	80	88	122	100	75
Actual weight for age[13]	102	89	98	106	104	97	130	132	123
Coefficient of energy absorption	0·85	0·97	0·96	0·88	0·96	0·68	0·86	0·74	0·82
Fat (g)	41	45	52	78	36	52	92	88	49
Protein (g)	69	32	43	90	46	92	74	68	49
Carbohydrate (g)	286	177	264	474	305	282	307	278	261
Zinc (mg)	9·1	4·5	6·1	12·6	5·8	14·3	8·9	12·6	7·4
Calcium (mg)	1066	637	673	1547	627	953	1513	809	653
Iron (mg)	8·4	3·4	5·5	17·3	9·8	13·2	8·4	7·0	8·3
Enzyme preparations:									
None taken	No	Yes	Yes	No	No	No	No	No	No
Non-enteric coated preparation	Yes	No	No	No	Yes	No	Yes	No	No
Enteric coated microsphere preparation	No	No	No	Yes	No	Yes	No	Yes	Yes

drinks were weighed on Salter electronic scales and weights recorded in a diary (after subtracting plate waste).[9] Children who were attending school recorded items of food and drink in a separate diary from which weights were later estimated. Compliance and technique were checked on home visits by a trained nurse technician. The available energy and macronutrient contents of the dietary records were calculated using a computerised version of the food tables of McCance and Widdowson.[10] From these tables the zinc, iron, and calcium intakes were also calculated and compared with the recommended amounts published by the Department of Health and Social Security (DHSS) (for calcium and iron) and the United States National Academy of Sciences (for zinc).[11 12] Energy intakes expressed as either MJ/24 hours or MJ/kg/24 hours for children with cystic fibrosis were compared with normal values derived from the WHO estimated average daily energy requirements for normal children on the basis of median weight for age and for kilogram of body weight.[13]

During the seven days of dietary recording, faeces were collected for three days using carmine dye capsules to mark a 72 hour sample. Three carmine capsules (300 mg) were swallowed with the evening meal, and another three capsules exactly 72 hours later. Stools were collected in polythene bags from the time of appearance of the dye in the faeces until the second appearance of the dye. The bag was kept in a sealed plastic container at room temperature until the collection was completed. It was then delivered to the laboratory and stored at 4°C until analysis. The gross energy content of the faeces was determined by bomb calorimetry using a ballistic bomb calorimeter (Gallenkamp Ltd) after freeze drying a sample of the homogenate.[14] Homogenisation was achieved by suspending the faeces in a known volume of water using Stomacher Lab-blender (AJ Stewart).

The coefficient of energy absorption was calculated using the formula: 1−(gross energy of faeces divided by the gross energy of the diet). Gross energy of the diet was calculated from the available energy by using the factors 5·65×g protein, 9·3×g fat, and 3·75×g carbohydrate and fibre.[15] Absorbed energy was calculated by multiplying energy intake with the coefficient of energy absorption. Dietary records were completed and faecal collections were successful in 20 of the 23 children.

10	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*
10·9	11·1	11·2	11·7	12·8	13·3	13·8	13·8	14·5	16·2	17·3
F	M	M	F	M	F	F	M	F	M	M
39·0	29·6	35·0	26·9	26·2	45·7	31·7	43·3	37·2	65·7	43·7
8·38	9·73	10·8	10·35	8·15	9·73	8·88	13·32	8·64	10·74	8·00
0·215	0·329	0·309	0·385	0·312	0·213	0·280	0·307	0·232	0·163	0·183
105	104	115	125	84	110	100	130	96	92	67
91	129	121	180	132	117	154	141	132	87	99
0·97	0·88	0·92	0·83	0·91	0·86	0·81	0·91	0·82	0·78	0·86
88	68	106	127	57	75	76	133	68	76	45
68	78	85	97	66	61	76	95	71	75	73
260	372	342	251	309	385	301	424	313	422	324
6·3	12·1	11·3	10·0	9·6	6·7	9·0	12·3	8·4	9·7	8·0
429	1286	1405	1851	1055	1018	676	1587	702	1012	874
7·4	15·5	13·4	8·9	15·9	7·7	10·4	12·8	11·1	10·9	13·0
Yes	No	No	No	No	No	No	No	No	No	No
No	No	No	Yes	No	Yes	Yes	No	Yes	Yes	Yes
No	Yes	Yes	No	Yes	No	No	Yes	No	No	No

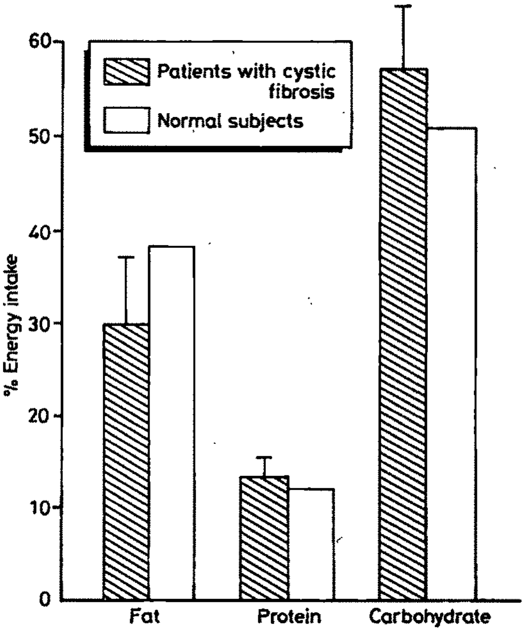


Fig 1 *Energy contributions from fat, protein, and carbohydrate as percentage of the total dietary energy intake in 20 children with cystic fibrosis compared with normals.*[9]

Data was analysed by the Minitab statistics programme.[16] Mean values for data were calculated (in most cases close to median values). Associations between variables were assessed by Spearman's rank and simple product correlation.

Results

Dietary records were completed and collections of faeces sucessfully carried out in 20 out of the 23 children (11 boys and nine girls). Their mean age was 11·1 years (range 5·3 to 17·3) and their Shwachman scores ranged between 57 to 94. Weight for age standard deviation scores ranged between −2·8 to +2·3 with a mean of −0·8. Seventeen out of the 20 children were taking enzyme replacements. In eight cases microsphere enteric coated preparations (either Pancrease or Creon) were used. There was no significant association between energy intake or absorption, and the type of enzyme replacement used. The three children not taking enzyme replacements had coefficients of energy absorption above 0·92.

ENERGY AND NUTRIENT CONTENTS OF DIETS

On average (SD) total 24 hour energy intakes were close to the WHO estimated requirements for normal children of median weight for age ((98·7% (20%)). Median (SD) energy intakes expressed/kg body weight/24 hours were on average 118·2 (24%) above those of normal children. On average 30·0% of the total daily dietary energy intake was from fat (2·25 g/kg), 13·2% (2·21 g/kg) from protein, and 56·3% (10·63 g/kg) from carbohydrate. The balance of macronutrients compared with recently published values for normal children is shown in fig 1.[9] When energy losses in the faeces were taken into account the mean absorbed energy intake was either 85·3% of the estimated normal requirement (for children of median weight for age) (SD 19·8%), or 101·9% (expressed as energy/kg) (SD 20·2%). There were significant correlations between absorbed energy intakes expressed as percentages of the normal estimated amount both for median weight for age ($r=0{\cdot}52$, $p<0{\cdot}05$) and energy/kg ($r=0{\cdot}56$, $p<0{\cdot}05$), and the proportion of fat in the diet, implying that children with a higher proportion of fat in their diets ate and absorbed proportionately more energy (fig 2).

ZINC, IRON, AND CALCIUM INTAKES

Seventeen out of the 20 children had inadequate zinc intakes compared with the recommended amounts,[12] and 13 out of the 20 had low iron intakes.[11] Only one child had a calcium intake less than that recommended for age.

MILK AND DIETARY SUPPLEMENTS

All 20 children drank whole milk and some also drank skimmed or semiskimmed milk. Fourteen children drank mainly whole milk, although in five cases skimmed milk was also consumed (usually with supplements). Six children drank mainly skimmed milk, all six also taking whole milk at times—for example, in coffee or tea. The energy and macronutrient contributions to the diet by whole milk, skimmed milk, and both combined are shown in table 2. For example, whole milk accounted for (on average) 10·9% of the daily dietary energy intake and 18·2%, 17·2%, and 5·5% of the fat, protein, and carbohydrate intakes by weight, respectively.

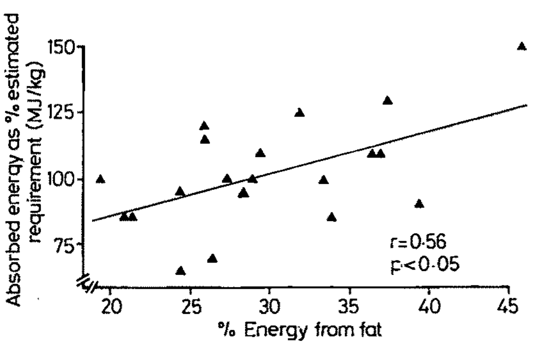


Fig 2 *Absorbed energy expressed as a percentage of estimated daily energy requirement (energy/kg), and the percentage of the total dietary energy intake from fat.*

Table 2 *Energy and macronutrient contributions from different milks and supplements*

	Total No	*Mean % daily dietary intake*			
		Energy	*Fat*	*Protein*	*Carbohydrate*
Whole milk	20	10·9	18·2	17·2	5·5
Skimmed milk	11	3·2	0·3	9·4	4·1
Total milk	20	12·6	18·7	22·4	7·8
Supplements	7	3·9	0	5·3	6·9

There were seven children who also took dietary supplements (Build-up, n=6; Maxijul, n=1; Polycal, n=1; Nesquick, n=1). Their standard deviation scores for weights and heights for age were not significantly different from those who were not taking supplements. The fraction of the total energy intake from supplements in the seven children was 3·9%. This compared with 10·9% from whole milk in all 20 children.

Discussion

The results of this survey suggest that many children with cystic fibrosis are still on low fat diets, but overall they seem to maintain energy intakes close to the estimated energy requirements for normal children. Using the WHO energy requirements tables[13] it is possible to estimate the daily energy needs of a population of children of average (median) weight for age. The tables also allow adjustment for children of different weights at particular ages by listing the energy requirements/kg body weight. In this study we have included both comparisons because there is no accepted method for estimating the true requirements of a group of undernourished children with a wasting disease like cystic fibrosis. In so far as the energy requirements of an individual subject are determined by the active tissue mass of that individual, it would perhaps seem more reasonable to compare the energy intakes of children with cystic fibrosis with those of normal children of the same weight—that is by energy/kg. When this is done, many of the children with cystic fibrosis have above average energy intakes (mean

118·2%) lending credence to the traditional observation that clinically stable children with cystic fibrosis often have voracious appetites.[1] This apparent increased energy intake presumably reflects increased energy demands either through energy losses in the stools or as a result of possible increased energy expenditure.[17] Interestingly, after adjusting for energy losses in the stools the absorbed energy was close to the average estimated energy requirement (mean 101·9%). Because the cost of catch up growth for both weight and height in the clinical context of malabsorption and pulmonary disease is unknown, however, it could be argued that energy requirements for a group of children with cystic fibrosis would be better estimated on the basis of a group of normal children of median weight for age. When this is done the apparent energy intakes of the children with cystic fibrosis are less than those calculated on the basis of energy/kg (mean 98·7%). After faecal energy losses were taken into account many children fell short of the estimated energy requirements (mean 89·1%).

We found no significant difference in the coefficients of energy absorption between children taking enzyme replacements as encapsulated microsphere preparations and those on other preparations, a surprising finding in view of cross over studies that have shown that the recently developed microsphere encapsulated preparations significantly reduce steatorrhoea when compared with the older pancreatic preparations.[18] It should be appreciated, however, that the subjects in the current study were unselected and examined cross sectionally. There was, perhaps, a tendency for children with less steatorrhoea and malabsorption to remain on the older preparations.

Though fat was often reduced in the children's diets there were increased fractions of carbohydrate and protein: indeed, mean protein intakes (2·21 g/kg/day) were over twice those recommended by WHO, not an uncommon finding in other nutritional surveys of patients with cystic fibrosis.[1 19] The associations between the proportions of fat and carbohydrate in the diet and energy intake suggest that diets with higher fat and lower carbohydrate fractions result in improved energy intakes. Fat has about twice the energy density (39 kJ/g) compared with carbohydrate (17 kJ/g), or protein (23 kJ/g). In addition, if the goal of nutritional rehabilitation in cystic fibrosis is the synthesis of fat stores from which energy can be used at times of infection, thus sparing lean body tissue breakdown, then the most economical source of this body fat is dietary fat. This is because the metabolic cost of converting dietary fat to body fat is low compared with that of converting carbohydrate or protein, and in the conversion of protein up to 30% of the energy value may be lost.[20]

Deficiencies of the elements calcium, zinc, and iron have in the past been suggested as having a role in the pathogenesis of some of the clinical features of cystic fibrosis.[21] In particular, low concentrations of iron have been associated with anaemia and low concentrations of zinc with failure of growth. Few studies, however, have looked at the dietary content of these elements. Though Bell *et al*[19] found the calcium contents of their diets for cystic fibrosis adequate, they noted that some patients had low iron concentrations; our study confirms their findings. The results should, however, be interpreted with caution as iron intakes as low as these have recently been measured in apparently healthy British school children.[9] Difficulties also arise with interpretation of the zinc intakes. Recommended intakes for zinc do not exist in the United Kingdom, and elsewhere in the world they vary widely; the United States[12] tends to recommend up to twice as much zinc as, for example, Canada.[22]

The study was not specifically designed to find out why children were on low fat diets, but it was our impression that in some cases the importance of increasing the fat content of the diet had not been sufficiently emphasised by medical staff or dietitians. Many families were eating what they regarded as normal diets, which included a variety of foods with reduced fat contents—in particular skimmed milk products. In the last few years such families have become more aware of the need to reduce fat in their diets to lessen the risks of atherogenesis.

We found that the children who had the highest fat and energy intakes were those taking more milk, in particular more whole milk. Those children who consumed mainly skimmed milk derived less nutritional benefit from this constituent of their diet (table 2). This is hardly surprising when the nutritional compositions of whole and skimmed milk are compared (whole milk energy/100 g—272 kJ; energy proportions—fat 52·6%, protein 20·3%, and carbohydrate 27·1%; skimmed milk energy/100 g: 138 kJ; energy proportions—fat 2·7%, protein 41·2%, and carbohydrate 56·8%).

In some cases milk was taken with a dietary supplement but the nutritional contribution from the supplements themselves was low. Examination of the dietary records showed that in most cases the supplements were taken irregularly. Nutritional intervention studies have suggested that dietary supplements can improve energy intakes.[23] The object of the present study, however, was not to test the value of such supplements but merely to survey their use and contribution to the diets of a random sample of children attending the cystic fibrosis clinic. To this extent we did not find them especially beneficial. We believe that whole milk has more to offer in terms of nutritional benefit, and perhaps more time should be spent in clinics emphasising the importance of whole milk in the diet instead of prescribing dietary supplements that can be expensive and are less readily available.

RM Buchdahl and JL Marchant were supported by grants from the CF Research Trust.

References

[1] Chase PH, Long MA, Lavin MH. Cystic fibrosis and malnutrition. *J Pediatr* 1979;**95**:337–47.

[2] Crozier DN. Cystic fibrosis. A not so fatal disease. *Pediatr Clin North Am* 1974;**21**:935–50.

[3] Gurwitz D, Corey M, Francis PWJ, Levison H. Perspectives in cystic fibrosis. *Pediatr Clin North Am* 1979;**26**:603–15.

[4] MacClusky IB, Canny GJ, Levison H. Cystic fibrosis: an update. *Pediatric Reviews and Communications* 1987;**1**:343–89.

[5] Bell L, Durie P, Forstner GG. What do children with cystic fibrosis eat? *J Pediatr Gastroenterol Nutr* 1984;**3**(suppl 1): 137–46.

[6] Shwachman H, Kulczycki LL. Long-term study of one hundred and five patients with cystic fibrosis. *Am J Dis Child* 1958;**96**:6–26.

[7] Cameron N. The methods of auxological anthropometry. In: Falline F, Tanner JM, eds. *Human growth*. Vol 2. New York: Plenum Press, 1978.

[8] Tanner JM, Whitehouse RH, Takaishi M. Standards from maturity for height, weight, height velocity and weight velocity: British children 1965—part 2. *Arch Dis Child* 1966;**41**:613–35.

[9] Wenlock RW, Disselduff MM, Skinner RK, Knight I. *The diets of British school children*. London: DHSS, 1986.

[10] Paul AA, Southgate DAT. *McCance and Widdowson's the composition of foods*. 4th ed. London: HMSO, 1978.

[11] Report by the Committee on Medical Aspects of Food Policy 1979. *Recommended daily amounts of food, energy and nutrient intakes for groups of people in the UK*. London: HMSO (DHSS No 19): 1985 (3rd impression).

[12] Food and Nutrition Board Committee on Dietary Allowances. *Recommended dietary allowances*. 9th ed. Washington: National Academy of Sciences, 1980.

[13] World Health Organisation. *Energy and protein requirements. Report of a joint FAO/WHO/UNU meeting*. WHO Tech Rep Ser no 724, Geneva: WHO, 1985.

[14] Miller DS, Payne PR. A ballistic bomb calorimeter. *Br J Nutr* 1959;**13**:501–8.

[15] Southgate DAT, Durnin JVGA. Calorie conversion factors. An experimental reassessment of the factors raised in the calculation of the energy value of human diets. *Br J Nutr* 1970;**24**:517–35.

[16] Ryan BF, Joiner BL, Ryan TA. *Minitab handbook*. 2nd ed. Boston: Duxbury Press, 1985.

[17] Buchdahl RM, Cox M, Fulleylove C, *et al*. Increased resting energy expenditure in cystic fibrosis. *J Appl Physiol* 1988;**64**: 1810–6.

[18] Beverley DW, Kelleher J, Macdonald A, Littlewood JM, Robinson T, Walters MP. Comparison of four pancreatic extracts in cystic fibrosis. *Arch Dis Child* 1987;**62**:564–8.

[19] Bell L, Linton WL, Corey ML, Durie P, Forstner G. Nutrient intakes of adolescents with cystic fibrosis. *Journal of the Canadian Dietetic Association* 1981;**42**:62–70.

[20] Pencharz PB. Energy intakes and low-fat diets in children with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1983;**2**:400–2.

[21] Silk DBA. Future directions in supplemental nutrition. In: Lawson D, ed. *Cystic fibrosis: horizons. Proceedings of the 9th International CF Congress, Brighton*. Chichester: John Wiley, 1984:99–114.

[22] Advisory Committee to Revise the Canadian Dietary Standard. *Recommended nutrient intakes for Canadians*. Ottawa: Health and Welfare Canada, 1983.

[23] Anonymous. Supplementary nutrition in cystic fibrosis. *Lancet* 1986;**i**:249–51.

Correspondence to Dr RM Buchdahl, Department of Child Health, King's College Hospital, London SE5 8RX.

Accepted 15 July 1988

Archives of Disease in Childhood, 1989, **64,** 379–382

Growth and very low birth weight

W H KITCHEN,*† G W FORD,* AND L W DOYLE*

**Departments of Obstetrics and Gynaecology and †Paediatrics, University of Melbourne, Australia*

SUMMARY Information on the likelihood of catch up growth in poorly grown very low birthweight children is sparse. The centiles for weight, height, and head circumference were recorded at both 2 and 5 years of age for 135 very low birthweight children and 42 normal birthweight children. At both ages significantly more children of very low birth weight were under the 10th centile for weight and height. Children of birth weight under 1000 g were more often under the 10th centile for weight at 5 years compared with those of birth weight 1000–1500 g. Mean incremental weight gain between 2 and 5 years was significantly less for very low birthweight children. Mean increment in weight from 2 to 5 years was less for very low birthweight children who had been under the 10th centile for weight at 2 years; children who had been under the 10th centile for height also had lower mean height increments. The growth centiles achieved by 2 years of age were useful predictors of poor growth at 5 years, with perinatal data of marginal importance. Only six of 43 (14%) children with a weight at 5 years of age under the 10th centile were small for gestational age at birth. Very low birthweight children who had a weight or height under the 10th centile at 2 years of age usually remained in this category at 5 years with no evidence of catch up growth.

In early childhood, many very low birthweight survivors (birth weight under 1501 g) are reported to grow poorly.[1 2] Parents of such children often ask whether catch up growth will occur but there is little information available on this subject for children born in the era of sophisticated neonatal intensive care.

To assist in counselling parents of poorly growing children of very low birth weight, we assessed the physical growth of a cohort of these children and a comparison group of normal birthweight children when aged 2 years and again at 5 years. The growth centile attained and incremental growth over this period were examined for evidence of catch up growth; we also looked for possible early predictors of poor growth at 5 years of age.

Patients and methods

The cohort of very low birthweight children comprised 154 consecutive survivors of birth weight under 1501 g born in The Royal Women's Hospital, Melbourne between 1 October 1980 and 31 March 1982. Anthropometric data were available at both 2 and 5 years for 135 children (87%), but for one of these children the height at 2 years was not available. Of the 19 children not included in the study, two were too disabled to measure weight and height accurately, six were untraced or the parents refused assessment, and 11 had growth data at 2 or 5 years only. The mean birth weight of children was 1183 g and mean gestational age was 29·3 weeks. Very low birthweight children with paired growth data were seen at the mean ages of 2·2 and 5·2 years, corrected for prematurity.

Sixty children of normal birth weight (birth weight over 2500 g) were selected for longitudinal study in a quasirandom fashion, using the terminal digits of the mother's unit record number. These normal birthweight children were born in the same hospital during the same years as the very low birthweight children. Growth data were available for 42 (70%) children at mean ages of 2·0 years and 5·1 years. One child of normal birth weight was too disabled to measure accurately, two had growth data at one age only, and 15 were untraced or the assessment was refused.

Weight, standing height, and occipitofrontal head circumference were measured in a standard fashion.[3] Centile positions for weight and height were derived from standards for an urban multiracial Australian community.[4 5] Centiles for head circumference were obtained from the composite charts of Nellhaus.[6] The increments in weight, height, and head circumference between the ages of 2 and 5 were computed.[7] Because the interval between assessments was not exactly three years in every child, the increments in growth between 2 and 5 years of age were divided by the time between assessments to calculate the average annual growth increment.

Data were analysed by computer using SPSSX package programs. Differences in proportions were analysed by corrected χ^2 tests; differences in normally distributed continuous data were compared by *t* tests. To compare data not normally distributed, Mann-Whitney U tests were used. McNemar tests were used to determine whether significant proportions of children changed from 2 to 5 years relative to the 10th centile for growth. Discriminant analysis was used to obtain predictors of growth measurements under the 10th centile at 5 years of age. In the three discriminant analyses the dichotomous dependent variables were weight, height, and head circumference at 5 years, respectively above or below the 10th centile. Perinatal independent variables included growth centiles at birth, birth weight, gestational age, use of mechanical ventilation, necrotising enterocolitis, recurrent apnoea, duration of ventilation and of oxygen treatment, bronchopulmonary dysplasia, day of lowest postnatal weight, social status, duration of maternal education, and immigrant status. Mothers were designated as immigrants if they were born in a country where English was not the first language. The additional independent variables available at 2 years of age included growth centiles at 2 years, the number of days of hospital readmission, number of hospital readmissions, and number of episodes of wheezing. A p value less than 0·05 on any statistical test was regarded as significant.

Results

Table 1 shows the number of children with size indices below the 10th centile. There were significantly more children of very low birth weight with weights and heights under the 10th centile at both 2 and 5 years but not for head circumference. For these children the proportion with a head circumference under the 10th centile increased significantly from 2 to 5 years (p=0·0002); over this period, children of birth weight 1000–1500 g deteriorated significantly (p=0·008) with a similar but non-significant trend for those of birth weight under 1000 g. A significant deterioration in head growth was not observed in the normal birthweight children; the proportions relative to the 10th centile did not change significantly for any other growth measurement between 2 and 5 years, either for the children of normal or very low birth weight.

Significantly more children of birth weight under 1000 g were below the 10th centile for weight and height at 2 years compared with children of birth weight 1000 to 1500 g; however, this difference persisted at 5 years only for weight.

Using the 3rd centile as a more stringent criterion for poor growth, at 5 years of age 27 out of 135 (20%) of the very low birthweight children were below this point for weight, 14 out of 135 (10%) for height, and 11 out of 135 (8%) for head circumference; 12 out of 135 (9%) of the very low birthweight children were under the 3rd centile for both weight and height. No child of normal birth weight was under the 3rd centile for any of these measurements.

We next investigated the centile ranking, rather than the percentage of children under the 10th centile (as was shown in table 1); children in both groups were compared using Mann-Whitney U tests. The very low birthweight children had significantly lower centiles for weight at 2 years (z=−5·90, p<0·0001), and at 5 years (z=−4·69, p<0·0001), for height at 2 years (z=−5·44, p<0·0001) and at 5 years (z=−3·57, p=0·004), but for head circumference only at 5 years (z=−2·85, p=0·004).

Table 1 *No (%) of children with size indices under the 10th centile at 2 and 5 years of age*

Group	*Weight*		*Height*		*Head circumference*	
	2 years	*5 years*	*2 years*	*5 years*	*2 years*	*5 years*
Normal birth weight (n=42)	0	2 (5)	0	2 (5)	0	3 (7)
Very low birth weight (n=135)	35 (26)	43 (32)	34 (25)*	31 (23)	4 (3)	17 (13)
	p=0·005†	p=0·009†	p=0·007†	p=0·02†	NS	NS
Very low birth weight:						
Birth weight 500–999 g (n=28)	16 (57)	16 (57)	13 (46)	9 (32)	0	5 (18)
Birth weight 1000–1500 g (n=107)	19 (18)	27 (25)	21 (20)*	22 (21)	4 (4)	12 (11)
	p=0·001†	p=0·003†	p=0·008‡	NS	NS	NS

*No height at 2 years for one child, birth weight >1000 g, normal height at 5.

†Normal birth weight compared with very low birthweight children.

‡Infants of birth weight 500 to 999 g compared with those of birth weight 1000 to 1500 g.

The mean incremental growth between the assessments at 2 and 5 years of age is shown in table 2. Increments in weight were significantly less in children of very low birth weight compared with those of normal birth weight, but were similar for height and head circumference, indicating no evidence of catch up in height or head growth and a significant deterioration in weight gain. Children of birth weight under 1000 g had similar growth increments compared with those of birth weight 1000 to 1500 g (table 2). Those children of very low birth weight who had weighed under the 10th centile at 2 years had significantly lower weight increments compared with the remainder; those who had been under the 10th centile for height at 2 years had significantly lower height increments (table 2).

Possible predictors of growth that was under the 10th centile at 5 years of age were determined using discriminant analyses. The corresponding growth centile achieved by 2 years was the most important clinical and statistical predictor; a few perinatal variables and one health variable accounted for a small percentage of the variance, which was of statistical rather than clinical significance. Predictors of a 5 year weight under the 10th centile were weight centile at 2 years (29·2% of variance, p=0·0001), birthweight centile (2·3% additional variance, p=0·007), immigrant status (2·4% additional variance, p=0·02), and the use of mechanical ventilation (2·9% additional variance, p=0·007). For 5 year old height under the 10th centile, predictors were the 2 year height centile (19·3% of variance, p=0·001) and immigrant status (2·4% additional variance, p=0·025). For the 5 year head circumference under the 10th centile, significant predictors were head centile at 2 years (28·3% of variance, p=0·0001) and the number of wheezing episodes in the first 2 years of life (2·6% additional variance, p=0·021).

Only six out of 43 (14%) children with a weight at 5 years under the 10th centile were also under the 10th centile for birth weight. There were 12 children who had birth weights under the 10th centile and by 5 years six remained in this category, four had grown normally, and two were untraced.

Discussion

Children of very low birth weight, judged by the centile attained in early childhood, have been reported to grow poorly in weight and height, with fewer problems with head growth.[1 8–12] Those of birth weight under 1000 g are even more likely to grow poorly in weight and height.[13 14] These reports, however, do not provide the data on incremental growth or growth velocity that are needed to assess whether poorly growing survivors of very low birth weight catch up in later childhood.

In our study, very low birthweight children at 2 and 5 years of age were significantly lighter and

Table 2 *Mean annual growth increments between 2 and 5 years*

Group	*Mean (SD) weight (kg/year)*	*Mean (SD) height (cm/year)*	*Mean (SD) head circumference (cm/year)*
Normal birth weight (n=42)	2·29 (0·84)	7·58 (1·21)	0·70 (0·33)
Very low birth weight (n=134)	2·00 (0·67) t=2·02 p=0·048	7·55 (1·02) NS	0·69 (0·23) NS
Very low birth weight:			
Birth weight <1000 g (n=28)	1·97 (0·74)	7·64 (0·96)	0·73 (0·23)
Birth weight 1000–1500 g (n=106)	2·02 (0·66) NS	7·52 (1·04) NS	0·68 (0·22) NS
Very low birth weight:			
Weight <10th centile at 2 years (n=35)	1·75 (0·49)		
Weight >10th centile at 2 years (n=100)	2·09 (0·70) t=−2·56 p=0·012		
Height <10th centile at 2 years (n=34)		7·13 (0·62)	
Height >10th centile at 2 years (n=100)		7·68 (1·09) t=−2·96 p=0·007	
Head circumference <10th centile at 2 years (n=4)			Insufficient for analysis

shorter than their normal birthweight controls. Moreover, compared with our own normal birthweight population, standards for a multiracial Australian urban population,[4] and the charts of Tanner *et al,*[3] those under the 10th and 3rd centiles for weight and height were substantially over represented. Children of birth weight under 1000 g were significantly lighter at 5 years compared with those of birth weight 1000 to 1500 g.

There was no convincing evidence of catch up growth for very low birthweight children between 2 and 5 years. Parents of these children who are growing poorly at 2 years may ask for reassurance that catch up growth will occur; rather than provide this reassurance, our data show that weight or height increments between 2 and 5 years are likely to remain below average, perpetuating poor growth.

We previously reported that very low birthweight children, born in the era when mechanical ventilation was not utilised and when survival prospects were lower (1966–70), attained near normal growth centiles at 14 years of age.[15] These children are not comparable with survivors of the intensive care era; consequently, the current cohort should be followed up to determine what changes in growth occur during puberty.

Significantly more children of very low birth weight had a head circumference under the 10th centile at 5 years compared with 2 years. We speculate that the decrease in centiles of these children may relate to their skulls assuming a less dolicocephalic shape from 2 to 5 years and are not necessarily a reflection of decreased brain growth.

Being under the 10th centile for any of the three size indices at 5 years was not dominantly determined by being under the 10th centile for that index at birth. The 43 children with weights under the 10th centile at 5 years included only six who were small for gestational age at birth. The centile attained for weight at 2 years was the predominant 'predictor' of poor weight gain over the next three years, with other factors of only marginal clinical importance.

With the increasing availability of synthetic growth hormone, it is likely that this treatment will be evaluated in children who do not have demonstrable growth hormone deficiency. Our study indicates that, without intervention, children of very low birth weight who are small at 2 years will generally remain so at 5 years. If a trial of growth hormone is contemplated these children provide a readily indentified risk group for poor growth; they can usually be identified by 2 years of age and they are unlikely to exhibit spontaneous catch up in weight or height over the next three years.

The work was supported in part by the National Health and Medical Research Council and the Royal Women's Hospital—3AW Clinical Research Foundation.

References

[1] Vaucher Y. Growth in the high risk newborn. In: Sell EJ, Brazleton TB, eds. *Follow-up of the high risk newborn—a practical approach.* Springfield: Charles T Thomas, 1980: 101–17.

[2] Hack M, Merkatz IR, Gordon D, Jones PK, Fanaroff AA. The prognostic significance of postnatal growth in very low-birthweight infants. *Am J Obstet Gynecol* 1982;**143:**693–9.

[3] Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity. British children 1965. *Arch Dis Child* 1966;**41:**454–71.

[4] Jones DL, Hemphill W, Meyers ESA. *Height, weight and other physical characteristics of New South Wales children. Part I. Children aged 5 years and over.* New South Wales: Government Printer, 1973.

[5] Jones DL, Hemphill W. *Height, weight and other physical characteristics of New South Wales children. Part II. Children under 5 years of age.* New South Wales: Government Printer, 1974.

[6] Nellhaus G. Head circumference from birth to 18 years. *Pediatrics* 1968;**41:**106–14.

[7] Roche AF, Himes JH. Incremental growth charts. *Am J Clin Nutr* 1980;**33:**2041–52.

[8] Gross SJ, Oehler JM, Eckerman CO. Head growth and developmental outcome in very low birth-weight infants. *Pediatrics* 1980;**71:**70–5.

[9] Kimble KJ, Ariagno RL, Stevenson DK, Sunshine P. Growth to 3 years among very low-birth-weight sequel-free survivors of modern neonatal intensive care. *J Pediatr* 1982;**100:**622–4.

[10] Ross G, Krauss AN, Auld PA. Growth achievement in low-birth-weight premature infants: relationship to neurobehavioral outcome. *J Pediatr* 1983;**103:**105–8.

[11] Tudehope DI, Burns Y, Callaghan M, Mohay H, Silcock A. The relationship between intrauterine and postnatal growth on the subsequent psychomotor development of very low birthweight (VLBW) infants. *Aust Paediatr J* 1983;**19:**3–8.

[12] Saigal S, Rosenbaum P, Stoskopf B, Milner R. Follow-up of infants 501 to 1500 gram birthweight delivered to residents of a geographically defined region with intensive perinatal care facilities. *J Pediatr* 1982;**100:**606–13.

[13] Hoskins EM, Elliot E, Shennan AT, Skidmore MB, Keith E. Outcome of very low birth-weight infants born in a perinatal center. *Am J Obstet Gynecol* 1983;**145:**135–40.

[14] Ford G, Rickards A, Kitchen WH, Ryan MM, Lissenden JV. Relationship of growth and psychoneurologic status in 2-year-old children of birthweight 500–999g. *Early Hum Dev* 1986;**13:** 329–37.

[15] Kitchen WH, Ryan MM, Rickards AL. Longitudinal study of very low birthweight infants: impairments, health and distance growth to 14 years of age. *Aust Paediatr J* 1987;**23:**335–8.

Correspondence to Dr WH Kitchen, Department of Obstetrics and Gynaecology, University of Melbourne, Parkville 3052, Australia.

Accepted 21 August 1988

Archives of Disease in Childhood, 1989, **64,** 383–387

Weight and age at menarche

O STARK,* C S PECKHAM,* AND C MOYNIHAN†

**Institute of Child Health, University of London, and †Academic Department of Radiotherapy, Royal Marsden Hospital, London*

SUMMARY In the National Child Development Study (1958 cohort) information on their age at menarche and their weights and heights measured at 7, 11, and 16 years was available for 4427 girls. The distribution of age at menarche was not influenced by social class. Weight adjusted for height did not play an important part in the timing of sexual maturation of the girls in the study. Relative weight (weight expressed as a percentage of standard weight) at the ages of 7 and 11 years explained only 3·2%, and 4·9%, respectively of the variation in age at menarche, and changes in relative weight between these two ages accounted for 2%. Girls with early menarche were more likely to be overweight at ages 7, 11, and 16 years than those with late menarche, although early menarche was also reported by girls who were underweight or of average weight. These findings support the hypothesis that in well nourished populations the relation between menarche and body size is largely regulated by genetic factors and that nutrition is less important.

Studies in experimental animals have suggested that nutrition has an important effect on sexual development.[1 2] In humans, however, such evidence is mainly circumstantial. Epidemiological and clinical studies show that pubertal development is delayed in undernourished populations[3] and in malnourished children,[4 5] and that early puberty is associated with overweight.[6]

In girls, menarche is an indicator of pubertal timing but the mechanism that controls the onset of puberty and triggers menarche is not known. It has been suggested that early menarche in obese girls may be due to overweight resulting from overeating.[6 7] Some studies do not support this hypothesis, however, and the association between overweight and menarche remains unclear.[8]

Using data derived from the National Child Development Study,[9] we describe the association between age at menarche and relative weight (weight adjusted for height) and estimate the incidence of early menarche in girls who were overweight and underweight at 7 and 11 years of age. As the data are longitudinal it was also possible to relate age at menarche to birth weight and to changes in relative weight between the ages of 7 and 11 years. The hypothesis[10] that nutrition plays a leading role in the timing of the menarche is discussed in the light of the findings of the study.

Method

The National Child Development Study (NCDS) is a longitudinal follow up study of all children in England, Scotland, and Wales who were born in one week in March 1958. The original cohort of nearly 17 000 was studied at birth and again at the ages of 7, 11, and 16 years. Information on health, education, family, and socioeconomic class was collected at each follow up visit.

At the medical examination when they were 16 years old, girls were asked at what age they had first menstruated. Of those who responded, 4427 had had their weight and height measured when they were 16, 3653 when they were 7, and 3675 when they were 11 years old. Complete information on age at menarche and weight and height at 7, 11, and 16 years of age was available for 3018 girls. The analysis of response rates and the assessment of expected weight for height have been previously described.[11] Relative weight, which is observed weight expressed as a percentage of the weight expected from a regression of log weight on log height, was calculated for each girl at each age. This assumes that expected weight=c(height)^p, where c and p are constants. Overweight was defined as weight that exceeded the expected weight by 20% (relative weight more than 120). In the previous study of prevalence of overweight[11] children from multiple births, illegitimate births, and immigrants were excluded, but in the current analysis the whole cohort was included.

The validity of recalled data about age at menarche was assessed by comparison with data from a study of growth in girls born in 1962 in Newcastle upon Tyne who were examined at half yearly intervals between the ages of 9 and 17 years.[12] These girls recorded the date of their first menstruation on a calendar. The cumulative frequency of age at menarche in both cohorts was compared up to the age of 16 years. Slightly more girls had earlier menarche in the NCDS than in the Newcastle study but the difference was not significant (Kolgorov-Smirnov two tailed test $p>0·1$) (table 1). Comparison after this age was not possible because 94 girls in the NCDS had not yet menstruated at the time of the interview, which took place shortly after their 16th birthday. The Newcastle upon Tyne survey continued up to the age of 17 years and the age at menarche was known for all the girls.

Table 1 *Age at menarche in the National Child Development Study (n=4427) and the Newcastle upon Tyne study (n=699)*

Age at menarch (years)	*National Child Development Study (cumulative %)*	*Newcastle upon Tyne study (cumulative %)*
−11	2·2	1·7
−12	15·4	11·2
−13	39·4	38·8
−14	73·1	71·1
−15	92·7	92·4
−16	97·7	98·9

Results

AGE AT MENARCHE AND SOCIAL CLASS

Social class had no significant effect on the distribution of age at menarche among the girls in the NCDS.

AGE AT MENARCHE AND RELATIVE WEIGHT

The relative weight distribution at 7, 11, and 16 years of age for each age at menarche is shown in table 2. To preserve the largest possible numbers in the marginal groups the data presented are cross-sectional and numbers vary among age groups. The numbers included at the age of 16 were larger than at younger ages because information on both age at menarche, and height and weight, were obtained at this examination. A larger proportion of girls with early menarche were heavier for their height at all ages than those with late menarche. The distribution of relative weight for each age at menarche followed a similar pattern at the ages of 7, 11, and 16 years.

Table 2 *Menarche and relative weight distribution at ages 7, 11, and 16 years*

Age at menarche (years)	*Age at measurement (years)*	*No of girls*	*Relative weight (%)*		
			<100%	*101–120*	*>120*
<11:	7	79	29	53	18
	11	76	31	49	20
	16	97	30	52	18
11:	7	478	46	44	10
	11	478	40	45	15
	16	585	36	49	16
12:	7	903	51	43	6
	11	898	54	34	12
	16	1066	46	44	11
13:	7	1244	58	38	5
	11	1245	60	33	8
	16	1494	56	38	7
14:	7	695	64	33	3
	11	722	68	24	6
	16	864	66	30	5
>14:	7	180	71	26	3
	11	181	73	24	3
	16	277	78	20	2
Not yet reached menarche:	7	74	72	27	1
	11	75	76	21	3
	16	94	93	7	0

BIRTH WEIGHT, RELATIVE WEIGHT AT 7 YEARS, AND AGE AT MENARCHE

Birth weight and menarche were not related. The relation between birth weight, relative weight at the age of 7, and age at menarche was complex (table 3). Relative weight above average (over 100) was found in a greater proportion of girls with birth weight above the 90th centile (58%) than below the 10th centile (33%). Within each birth weight group relative weight over 100 was more common among girls with early menarche than those with late menarche.

CHANGES IN RELATIVE WEIGHT BETWEEN THE AGES OF 7 AND 11 YEARS, AND THE AGE AT MENARCHE

The association between the age at menarche and changes in relative weight during the period preceding the onset of menstruation (7–11 years) was weak. In 106 girls whose relative weight remained above 120, 36 (34%) reported menarche before the age of 12 and similar early menarche was also reported by 13 (22%) of 60 girls whose relative weight was reduced from above 120 to below 120; this difference was not significant ($p<0{\cdot}1>0{\cdot}05$). Likewise the difference in the proportion of girls with early menarche (17 of 267, 6%) who remained underweight (relative weight less than 90) and those whose relative weight increased from below 90 to above 90 (18 of 170, 11%) was not significant ($p>0{\cdot}1$). For the whole NCDS population the proportion of variance explained by changes in relative weight between 7–11 years was 2% and was significant ($p<0{\cdot}0005$).

VARIATION IN AGE AT MENARCHE EXPLAINED BY WEIGHT, HEIGHT, AND RELATIVE WEIGHT

Weight (not corrected for height) at the ages of 7 and 11 years explained 6·5% and 18%, respectively, of the total variance in the age of menarche, whereas weight changes between the ages of 7 and 11 years explained 13%. The proportion of variance explained by relative weight, however, was smaller than that explained by weight or height independently (table 4). This difference can also be illustrated by correlation coefficients between age at menarche and weight, height and relative weight, which were −0·25, −0·19, and −0·18 at the ages of 7 years, and −0·43, −0·39, and −0·22 at the age of 11 years. These findings reflect the fact that—during growth—height and weight continue to increase, but relative weight may increase, decrease, or remain the same.

Table 3 *Association between relative weight at age 7, birth weight, and age at menarche*

Total No of subjects	*Birth weight centiles*	*% With relative weight above average at 7 years old by age at menarche (years)*				
		Total %	*<12*	*12*	*13*	*≥14*
267	<10	33	52	28	31	34
432	10–24	43	57	47	40	34
835	25–49	42	49	48	38	33
753	50–74	44	64	49	42	31
481	75–89	46	64	51	42	39
313	>90	58	64	63	57	46

Thirty one girls with gestational ages below 30 and above 44 weeks have been excluded.

Table 4 *Percentage variation in age of menarche explained by relative weight, weight, and height*

Age (years)	*Relative weight*	*Weight*	*Height*
7	3·2	6·5	3·5
11	4·9	18·0	15·1
Change between the ages of 7 and 11	2·0	13·1	

All differences are significant ($p<0{\cdot}0005$).

Discussion

In our study the association of early menarche and increased weight for height begins well before the onset of puberty, and persists into late adolescence. This is consistent with recently published results from a longitudinal study of 78 boys,[13] which showed that those who matured early were already heavier at 6 months of age. Studies reviewed by Tanner[14] also suggested that early puberty was associated with increased body size throughout childhood.

We have found that 18% of girls with menarche before the age of 11 years were overweight at the age of 7, but only 3% of those with menarche after the age of 14. Wolff attributed advanced sexual maturation in overweight girls to the influence of excessive energy intake on growth.[6] Frisch proposed that the onset of menstruation was dependent on attainment of a critical body weight for height that represents a critical composition of relative fatness, and that menarche occurs early in obese girls because they achieve this critical relative weight at an earlier age.[7] Her hypothesis (although widely publicised) has not been supported by the results of other studies.[8 15–17] Garn and Bailey analysed data from 550 mother/daughter pairs and showed that the correlation coefficient between the mothers' fatness and menarche was −0·11 and the daughters' fatness and menarche was −0·14; the correlation between mothers' and daughters' menarche was 0·25, and after correction for fatness was 0·23.[18] They concluded that the degree of fatness in girls had little effect on the association between the mothers' and daughters' ages of menarche.

Although early menarche was more common in overweight girls in this study, it also occurred in those who were underweight or whose relative weight declined between 7 and 11 years of age. Relative weight at the ages of 7 and 11 years explained only 3·2 and 4·9% of the variation in age at menarche, and changes in relative weight between these two ages accounted for 2%. These findings indicate that weight for height did not play an important part in the timing of sexual maturation. The weak association between relative weight and age at menarche makes it unlikely that nutrition had a decisive influence on the timing of menarche. If nutritional factors do have any effect on the timing of puberty they seem more likely to be important before the age of 7 when the association between relative weight and menarche is established. Liestol, who studied secular changes in the age at menarche, also considered that the influence of environment in the first years of life was the most important.[19]

Information on diet was not collected in our study but Mills *et al* in the United States found no correlation between pubertal status in 14 year old boys and their intake of calories, protein, and other nutrients, and diet recorded every three years from birth failed to explain increased weight in those who matured early.[13] He suggested that there may be a factor present in early life that mediates growth and the onset of puberty, and that the association between the timing of puberty and body size may be controlled by genetic influence. The influence of heredity on the early origin of obesity in girls with early menarche needs to be assessed in a more detailed study. Our finding that relative weight at the age of 7 years was associated with birth weight and age at menarche, and that birth weight and menarche were not, needs further clarification.

The relative importance of environmental and genetic factors varies among populations. The delaying effect of malnutrition and poverty on sexual maturation has been observed in many developing countries.[3] In industrialised societies the age at menarche has decreased over the past 100 years and this trend has been attributed mainly to improvements in health and nutrition.[20] There is evidence that this trend is not continuing in some European countries, including Great Britain.[3] The children in our study were born in 1958 and grew up during a time of economic prosperity when there was an adequate national food supply. This may explain why the distribution of age at menarche was not influenced by social class and that nutritional factors were not decisive for the timing of menarche. Marshall proposed that if 'environment provides requirements for good nutrition and health the variability of the menarcheal age within the population may be mainly due to genetic factors.'[21] The findings from NCDS are consistent with this hypothesis.

We thank the staff of the National Children's Bureau for their help, Dr T Ades for statistical advice, and Professor June K Lloyd for her helpful comments.

References

[1] Cameron JL, Hansen PD, McNeil TH, *et al.* Metabolic cues for the onset of puberty in primate species: In: Venturoli S, Flamigni C, Givens J, eds. *Adolescence in females.* Chicago: Year Book Medical Publishers, 1985:59–78.

[2] Foster DL, Olster DH, Yellow SM. Neuroendocrine regulation of puberty by nutrition and photoperiod: In: Venturoli S, Famigni C, Givens J, eds. *Adolescence in females.* Chicago: Year Book Medical Publishers, 1985:1–21.

[3] Eveleth PB, Tanner JM, eds. *Worldwide variation in human growth.* Cambridge: Cambridge University Press, 1976.

[4] Dreizen S, Spirakis CN, Stone RE. A comparison of skeletal growth and maturation in undernourished and well-nourished girls before and after menarche. *J Pediatr* 1967;**70:**256–63.

[5] Kulin HE, Bwibo N, Mutie D, Med M, Santner SJ. The effect of chronic childhood malnutrition on pubertal growth and development. *Am J Clin Nutr* 1982;**36:**527–36.

[6] Wolff OH. Obesity in childhood. A study of the birth weight, the height and the onset of puberty. *Q J Med* 1955;**24:**109–22.

[7] Frisch RE. Critical weight at menarche, the initiation of the adolescent growth spurt, and control of puberty. In: Grumbach MM, Grave GD, Mayer FE, eds. *Control of the onset of puberty.* New York: John Wiley, 1974:403–23.

[8] Trussell J. Statistical flaws in evidence for the Frisch hypothesis that fatness triggers menarche. *Hum Biol* 1980;**52:**711–20.

[9] Fogelman K. *Growing up in Great Britain.* National Children's Bureau Series. London: Macmillan, 1983.

[10] Cheek DB. Body composition, hormones, nutrition and adolescent growth. In: Grumbach MM, Grave GD, Mayer FE, eds. *Control of the onset of puberty.* New York: John Wiley, 1974:424–42.

[11] Peckham CS, Stark O, Simonite V, Wolff OH. Prevalence of obesity in British children born in 1946 and 1958. *Br Med J* 1983;**286:**1237–42.

[12] Billewicz WZ, Fellowes HM, Thompson AM. Menarche in Newcastle Upon Tyne girls. *Ann Hum Biol* 1981;**8:**313–20.

[13] Mills JL, Shiono PH, Shapiro LR, Crawford PB, Rhoads GG. Early growth predicts timing of puberty in boys: results of a 14-year nutrition and growth study. *J Pediatr* 1986;**109:**534–47.

[14] Tanner JM. Factors affecting the rate of growth and the age at puberty. *Growth at adolescence.* Oxford: Blackwell Scientific Publications, 1962:94–155.

[15] Cameron N. Weight and skinfold variation at menarche and the critical body weight hypothesis. *Ann Hum Biol* 1976;**3:**279–82.

[16] Garn SM, La Velle M, Pilkington JJ. Comparisons of fatness in premenarcheal and postmenarcheal girls of the same age. *J Pediatr* 1983;**103:**328–31.

[17] Katch FI, Spiak DL. Validity of the Mellits and Cheek method for body-fat estimation in relation to menstrual cycle status in athletes and non-athletes below 22 per cent fat. *Ann Hum Biol* 1984;**11:**389–96.

[18] Garn SM, Bailey SM. The genetics of maturational processes.

In: Falkner F, Tanner JM, eds. *Human growth 1.* London: Baillière Tindall, 1978:307–30.
[19] Liestol K. Social conditions and menarcheal age: the importance of early years of life. *Ann Hum Biol* 1982;9:521–37.
[20] Van Wieringen JC. Secular growth changes. In: Falkner F, Tanner JM, eds. *Human growth 2.* London: Baillière Tindall, 1978:445–73.
[21] Marshall WA. Puberty. In: Falkner F, Tanner JM, eds. *Human growth 2.* London: Baillière Tindall, 1978:141–81.

Correspondence to Dr O Stark, Institute of Child Health, 30 Guilford Street, London WC1N 1EH.

Accepted 23 August 1988

Archives of Disease in Childhood, 1989, **64,** 388–394

Outcome of neonatal necrotising enterocolitis: results of the BAPM/CDSC surveillance study, 1981–84

S R PALMER,* A BIFFIN,* AND H R GAMSU†

**Public Health Laboratory Service Communicable Disease Surveillance Centre, Cardiff, and †King's College Hospital Medical School, London*

SUMMARY Neonatologists in 100 special care baby units in the United Kingdom and Ireland collaborated in a four year surveillance study of neonatal necrotising enterocolitis. The average overall annual reporting rate of necrotising enterocolitis for infants in England and Wales was 0·3/1000 live births, but ranged from 9·5/1000 live births in infants weighing less than 1000 g at birth to 0·2/1000 live births in infants weighing 2500 g or more. There were more deaths among girls, infants who weighed less than 1500 g at birth, those whose bleeding was abnormal or who had low peripheral platelet counts, infants with Gram negative bacteraemia, and very low birthweight infants who developed it during the first few days of life. In both boys and girls, and in all birthweight groups, operation was associated with increased mortality.

National surveillance of necrotising enterocolitis was set up by the British Association of Perinatal Medicine (BAPM) and the PHLS Communicable Disease Surveillance Centre (CDSC) in 1980.[1] The objectives were to describe the clinical features of necrotising enterocolitis, to monitor its pattern of occurrence, and to study factors associated with mortality. A pilot study of a clinical reporting scheme began in July 1980, and the definitive scheme began in July 1981 and ended in July 1984. The main findings of the first two years of the study were that outbreaks of necrotising enterocolitis occurred in six neonatal units, there was an inverse relationship between birth weight and age at onset, and there were more deaths among girls.[1] We now report the final results of the project.

Method of evaluation

Neonatologists who were members of the BAPM working in 100 neonatal units were asked to report all cases of necrotising enterocolitis diagnosed in their units to the CDSC using forms that requested data on main clinical features, date of birth, sex, birth weight, gestational age, date of onset of symptoms of necrotising enterocolitis, outcome, evidence of infection, and findings at operation or necropsy, or both. Criteria for reporting necrotising enterocolitis were the presence of at least two of the four following features: abdominal distension; blood in the faeces; hypotonia, lethargy or apnoeic episodes; and pneumatosis cystoides intestinalis. Cases were considered confirmed if they had either pneumatosis cystoides intestinalis, gas in the portal venous system or free air in the abdomen on abdominal radiograph, or histological evidence of necrotising enterocolitis.

From July 1981 to December 1982 cases from 60 units were reported. Neonatologists in the remaining 40 units were sent a questionnaire to ascertain if any cases of necrotising enterocolitis had been diagnosed; 23 (58%) replied and in 20 (87%) of these cases of necrotising enterocolitis had been diagnosed but not reported. After the questionnaire had been sent, reports were received from 15 of the 40 units until July 1984 including seven units that had not replied to the questionnaire.

Infants below the 10th centile for distribution of birth weight for gestational age were identified using published centile charts.[2] Data on live births were obtained from the Office of Population Censuses and Surveys.[3] Statistical comparisons were by χ^2 with Yates's correction and Fisher's exact test.

Results

Reports of 240 confirmed, and 158 unconfirmed, cases of necrotising enterocolitis were received. In

219 confirmed cases (91%), pneumatosis cystoides intestinalis was present. Of the remaining 21 confirmed cases, seven were confirmed on histological examination and 14 others were reported to have intestinal perforations or gas in the portal vein. Of the 158 unconfirmed cases, 97 had visible blood in the faeces (61%), and 24 (15%) had occult blood together with either abdominal distension or systemic signs, or both. Only 20 (13%) were diagnosed only by the presence of abdominal distension and systemic signs.

BIRTH WEIGHT AND GESTATIONAL AGE

The distribution according to birth weight and gestational age of confirmed and unconfirmed cases is shown in tables 1 and 2. The birthweight distribution of all infants born in England and Wales in 1982 is shown in table 3 for comparison. Incompleteness of reporting does not permit the calculation of the incidence of necrotising enterocolitis, but the average yearly birthweight specific reporting rates give an indication of the relative incidence of necrotising enterocolitis within birthweight groups.

Table 1 *Deaths among confirmed and suspected cases by birth weight*

Birth weight (g)	*Confirmed cases*			*Unconfirmed cases*		
	Total No	*No of deaths (%)*	*Outcome unknown*	*Total No*	*No of deaths (%)*	*Outcome unknown*
<750	10	4 (40)	0	9	3 (33)	0
750–999	36	15 (42)	0	26	3 (12)	0
1000–1249	42	14 (33)	0	27	2 (7)	0
1250–1499	34	15 (44)	1	17	1 (6)	0
1500–1999	38	5 (13)	1	32	1 (3)	0
2000–2499	25	3 (12)	3	12	0	1
≥2500	45	4 (9)	2	33	0	1
Not known	3	2 (67)	0	0	0	0
Total:						
<1500	122	48 (39)	1	79	9 (11)	0
≥1500	108	12 (11)	6	77	1 (1)	2
All cases	233	62 (26)	7	156	10 (6)	2

Table 2 *Deaths among confirmed and suspected cases by gestational age*

Gestational age (weeks)	*Confirmed cases*			*Unconfirmed cases*		
	Total No	*No of deaths (%)*	*Outcome unknown*	*Total No*	*No of deaths (%)*	*Outcome unknown*
≤28	59	21 (36)	0	40	6 (15)	0
29–30	40	17 (42)	2	26	3 (12)	0
31–32	46	12 (26)	0	22	1 (4)	0
33–36	41	6 (15)	3	27	0	1
≥37	40	3 (8)	2	36	0	1
Not known	7	3 (43)	0	5	0	0
Total	233	62 (27)	7	156	10 (6)	2

Table 3 *Confirmed cases in England and Wales 1981–84, and total live births in England and Wales, 1982*

Birth weight (g)	*No (%) with confirmed necrotising enterocolitis 1981–84*	*Total live births 1982 (% with necrotising enterocolitis)*	*Average annual reporting rate/1000 live births*
<1000	41 (20)	1442 (0·002)	9·5
1000–1499	70 (34)	3330 (0·006)	7·0
1500–1999	36 (18)	7529 (1·3)	1·6
2000–2499	22 (11)	27 632 (4·6)	0·3
≥2500	35 (17)	558 646 (93)	0·2
Total	204 (100)	598 579 (100)	0·3

The average annual reporting rate for confirmed necrotising enterocolitis ranged from 9·5/1000 live births among those that weighed less than 1000 g at birth to 0·2/1000 live births among those that weighed 2500 g or more.

The mortality among very low birthweight (VLBW) infants (those who had weighed less than 1500 g at birth) who were confirmed as having necrotising enterocolitis was 48/122 (39%). This was significantly higher than the 12 of 108 (11%) among infants who had weighed 1500 g or more at birth ($p<0{\cdot}001$, table 1). In confirmed cases, as the birth weight increased the mortality remained constant until 1500 g, when it dropped by 67%. In the unconfirmed cases there was a steady fall in mortality as birth weight increased. The mortality increased steadily as gestational age decreased until 29–30 weeks' gestational age in confirmed cases (table 2). Of the 192 singleton confirmed cases, 38 (20%) were below the tenth centile of weight for gestational age; mortality among these infants was not increased.

OUTCOME BY CLINICAL FEATURES

One VLBW infant and 11 other confirmed cases had only pneumatosis cystoides intestinalis and blood in the faeces, but no abdominal distension or tenderness or systemic signs, and none died. VLBW infants who were confirmed cases and who had an abnormal bleeding tendency or low peripheral platelet counts ($<100\times10^9$/l) had a higher mortality (20 of 38) compared with other VLBW infants (28 of 84, $p=0{\cdot}07$).

Infants who had weighed 1500 g or more at birth with abnormal bleeding or low platelet counts also had a higher mortality (nine of 24 compared with five of 87, $p<0{\cdot}001$). Sixteen of 37 VLBW infants with bacteraemia died compared with 32 of 85 who did not develop bacteraemia ($p=0{\cdot}7$), and three of 19 who had weighed 1500 g or more at birth who developed bacteraemia died compared with nine of 89 who did not ($p=0{\cdot}4$). The commonest organisms isolated from blood were *Staphylococcus epidermidis* and *Escherichia coli* (table 4). The mortality for VLBW confirmed cases with Gram negative bacteraemia (11 of 17) was significantly higher than for infants from whose blood other organisms had been isolated (five of 20, $p=0{\cdot}04$). Similarly, infants who had weighed 1500 g or more at birth who developed Gram negative bacteraemia had a significantly higher mortality (three of six compared with none of 13, $p=0{\cdot}02$).

One third of the confirmed cases had operations (table 5); the mortality among these cases was almost twice that among other infants ($p=0{\cdot}016$). This was most pronounced among infants who had weighed 1500 g or more at birth. Details of the indications for operation were not collected in the study, but in 164 confirmed cases there was no report of an abdominal radiograph showing free gas in the abdomen. Seven of 30 of the infants who had operations died, compared with 20 of 134 who did not ($p=0{\cdot}28$).

Among unconfirmed cases the mortality for VLBW infants and those who had weighed 1500 g or more at birth was 11% and 1% (table 1). Uncon-

Table 4 *Deaths among confirmed and suspected cases by organism isolated from blood*

Organism	*Confirmed cases*		*Unconfirmed cases*	
	Total No	*No of deaths*	*Total No*	*No of deaths*
S epidermidis	14	1	9	0
E coli	13	7	2	1
Staphylococcus aureus	6	1	2	0
Clostridium species	6	4	1	0
Pseudomonas species	5	5	1	0
Streptococcus species	5	1	3	2
Serratia species	1	1	0	0
Klebsiella species	3	1	3	2
Candida	1	0	0	0
Anaerobic diphtheroids	1	0	0	0
Bacteroides species	0	0	1	0
S epidermidis and Klebsiella species	1	0	0	0
S epidermidis and Bacteroides species	1	0	0	0
S epidermidis and diphtheroids	0	0	1	0
Total	57	21	23	5

firmed cases among VLBW infants with abnormal bleeding or low platelet counts had a significantly higher mortality: six of 22 compared with three of 57 (p=0·01). Five of 20 VLBW unconfirmed cases that developed bacteraemia died, compared with four of 59 that did not (p=0·05). Three of nine VLBW unconfirmed cases that had operations died, compared with only five of 65 that did not (p=0·05).

AGE AT ONSET

Age at onset of confirmed cases of necrotising enterocolitis ranged from 1 to 138 days, and was inversely related to birth weight. The median age of onset for infants who had weighed less than 750 g, 750–999 g, 1000–1249 g, 1250–1499 g, 1500–1999 g, 2000–2499 g, and 2500 g or more at birth was 15, 15, 12, 8, 10, 5, and 3 days, respectively. In VLBW infants with confirmed necrotising enterocolitis the median age of onset was 11 days and mortality decreased steadily as the age of onset increased. In infants who were heavier at birth no trend was found (table 6).

SEX

The mortality among girls with confirmed necrotis-

Table 5 *Deaths among confirmed cases by birth weight, sex, and whether they underwent operation*

Birth weight (g)	*Sex*	*Number operated on*			*Number not operated on*			*Total number*		
		Total No	*No of deaths (%)*	*Outcome unknown*	*Total No*	*No of deaths (%)*	*Outcome unknown*	*Total No*	*No of deaths (%)*	*Outcome unknown*
<1500	Male	23	10 (43)	0	27	6 (21)	1	50	16 (32)	1
	Female	20	10 (50)	0	47	19 (40)	0	67	29 (43)	0
≥1500	Male	18	2 (10)	2	38	3 (8)	0	56	5 (9)	5
	Female	15	5 (33)	1	36	2 (5)	0	51	7 (14)	1
Unknown	Male	0	0	0	0	0	0	0	0	0
	Female	1	1 (100)	0	2	1 (50)	0	3	2 (67)	0
Total:										
<1500		43	20 (47)	0	74	25 (33)	1	117	45 (38)	1
≥1500		33	7 (22)	3	74	5 (8)	0	107	12 (11)	6
	Male	41	12 (30)	2	65	9 (14)	1	106	21 (20)	6
	Female	36	16 (43)	1	85	22 (26)	0	121	38 (31)	1

It was not recorded whether six babies had operations, and the outcome was not known for three other boys. Five weighed <1500 g (two girls, one death; three boys, one death), and four weighed ≥1500 g (one girl, survived; three boys, unknown).

Table 6 *Deaths among confirmed cases by birth weight, sex, and age at onset of necrotising enterocolitis*

Birth weight (g) and sex	*Age at onset (days)*									*Total*		
	0–6			*7–13*		*14–20*		*≥21*				
	Total No	*No of deaths (%)*	*Outcome unknown*	*Total No*	*No of deaths (%)*	*Total No*	*No of deaths (%)*	*Total No*	*No of deaths (%)*	*Total No*	*No of deaths (%)*	*Outcome unknown*
<1500:												
Male	13	8 (62)	1	12	4 (33)	11	2 (18)	15	3 (20)	51	17 (32)	1
Female	21	10 (48)	0	21	11 (52)	7	4 (57)	19	5 (26)	68	30 (44)	0
≥1500:												
Male	34	4 (12)	4	12	0	2	1 (50)	8	0	56	5 (9)	4
Female	35	5 (14)	1	12	1 (8)	2	0	3	1 (33)	52	7 (13)	1
Total:												
<1500	34	18 (53)	1	33	15 (45)	18	6 (33)	34	8 (24)	119	47 (39)	1
≥1500	69	9 (13)	5	24	1 (4)	4	1 (25)	11	1 (9)	108	12 (11)	5
Male	47	12 (26)	5	24	4 (17)	13	3 (23)	23	3 (13)	107	22 (20)	5
Female	56	15 (27)	1	34	13 (38)	9	4 (44)	23	6 (26)	122	38 (32)	1

Age at onset was not recorded for three babies who weighed <1500 g (two boys and a girl, the girl died) and for one boy who weighed ≥1500 g (outcome not recorded). Birth weight was not recorded for one girl aged 7–13 days who died and one aged ≥21 days who survived. Neither were recorded for one further girl who died.

ing enterocolitis of 40 of 124 (32%) was higher than the 22 of 109 (20%) among boys (p=0·05, table 5), and this was not accounted for by differences in the distribution of birth weight or gestational age. Of VLBW boys, 23 of 50 (46%) had operations compared with 20 of 67 (30%) girls. In the VLBW girls the increased mortality was seen particularly in those who did not have operations: 19 of 47 compared with six of 27 (p=0·18), but in those who had weighed 1500 g or more at birth it was among those who did have operations, although the numbers were so small (five of 15 compared with two of 18) that this difference might not be significant. When mortality was examined by age at onset of necrotising enterocolitis, the rate for VLBW girls was higher in each period except for onset in the first week of life, when there was a higher rate among boys (table 6) and this applied both to those who had operations and those who did not.

FINDINGS AT OPERATION OR NECROPSY

Histological findings at operation or necropsy, or both, were recorded for 72 of the 108 confirmed cases that had operations or died. In 24 cases only the small bowel was diseased; the sites of the lesions were: jejunum (n=2), terminal ileum only (n=10), ileum (n=8), jejunum and terminal ileum (n=1), and the whole of the small bowel (n=3). In 12 cases the large bowel alone was diseased, and the sites of the lesions were: ascending colon (n=1), ascending and transverse colon (n=2), transverse colon (n=1), sigmoid colon (n=7), and rectum (n=1). In 24 cases both small and large bowel were diseased, and the sites of the lesions were: the whole of the small and large bowel (n=8), the terminal ileum and caecum (n=4), the terminal ileum and colon (n=8), and the caecum and colon (n=4). The colon seemed more likely to be diseased in infants who had been heavier at birth, but this difference was not significant.

Discussion

Population surveillance based on reporting by physicians is a useful method of characterising diseases of unknown aetiology—for example, Reye's syndrome.[4 5] Surveillance data may show epidemiological and clinical patterns that warrant more detailed study, and programmes are being developed to study several newly recognised diseases of children.[6] In our study, which relied upon members of the BAPM initiating reports, there was underreporting and no reports were received from a few large neonatal units. The survey of units that did not send any reports during the first part of the study suggested that at least 20% of units had diagnosed cases of necrotising enterocolitis. For this reason rates of reporting based on national birth rates must be considered only a minimum estimate of incidence. These estimates, however, do emphasise the strong association between low birth weight and necrotising enterocolitis. Our experience with clinical surveillance confirms the need to encourage more complete reporting by regularly contacting clinicians and confirming the presence or absence of cases by methods such as those now used for Reye's syndrome in the United Kingdom.[7]

The highest mortality was associated with very low birth weight and low gestational age, although surprisingly a trend of decreasing mortality with increasing birth weight was not seen within the VLBW group with confirmed necrotising enterocolitis; the mortality among these infants compares favourably with earlier studies.[8-11] In VLBW infants, onset in the first week of life and an abnormal bleeding tendency or low platelet counts were associated with significantly higher mortality. The mortality among infants with evidence of intrauterine growth retardation was not increased. Gram negative bacteraemia was associated with a higher mortality and this observation might be used to support the use of prophylactic antibiotics. It should be borne in mind, however, that antibiotic resistant organisms may cause severe morbidity.[12] Strict infection control, especially attention to hand washing, must be maintained at all times.[13 14]

Infants who had operations had a significantly higher mortality. A possible explanation for this is that operation was only undertaken when the clinical condition was deteriorating, and when the outcome was poor. In this surveillance study we did not collect data on the indications for operation, but the fact that mortality was not lowered by operation in this and other studies[11 15] indicates the urgent need for controlled trials to evaluate the role of operation in the management of necrotising enterocolitis. Kliegman and Fanaroff[16] suggest that in the absence of intestinal perforation (shown on abdominal radiographs or by paracentesis) operation should be avoided; even in infants with perforations, conservative management may be successful.[17] In our study 38% of infants who had operations were not reported as having radiological evidence of perforation. In infants considered to have necrotising enterocolitis without pneumatosis cystoides intestinalis the outcome without operation was excellent, and referral of such cases to a paediatric surgeon would not generally be indicated.

The persistently higher mortality among girls is intriguing and cannot be explained by their lower birth weights and gestational ages. In VLBW infants who had necrotising enterocolitis confirmed during the first week of life there was an increased mortality, but in infants who did not develop necrotising enterocolitis until the second or third week mortality fell steadily among boys but increased among girls. One possible explanation is that a higher proportion of girls survived other more common life threatening diseases associated with low birth weight and prematurity, but that these ill survivors were less able to withstand the additional stress of necrotising enterocolitis. This may also explain the finding that VLBW girls were less likely to have operations, perhaps because they were considered less able to withstand operation, although the mortality was higher among those who did have them.

The clinical criteria for reporting were broad enough to include infants who did not have pneumatosis cystoides intestinalis. Whether these unconfirmed cases, who usually presented with abdominal distension and blood in the stools, did have necrotising enterocolitis is debatable[18] although histologically proved necrotising enterocolitis can occur without radiological features.[19] Infants in whom the disease was not confirmed were more mature at birth, and developed less serious disease earlier in life. Possibly these cases were diagnosed and treated before radiological signs became apparent, or in these cases the disease was caused by bacteria that do not produce gas. Some cases may have been associated with feeding intolerance.[18] In our study clinicians were not asked to distinguish suspected from confirmed cases so that all cases were diagnosed and managed as necrotising enterocolitis and most suspected cases did have abdominal distension and blood in the stools. Infants with gastrointestinal symptoms attributed to other diseases would not have been reported to us. Bell *et al*[20] have proposed a clinical staging system for necrotising enterocolitis, but the criteria for inclusion as definite, as opposed to suspected, necrotising enterocolitis are not sufficiently specific to apply to our cases. Most of our suspected cases, however, had gross blood in the stool and these seem closer to their stage II (definite) than stage I (suspect).

It may be that both confirmed and suspected necrotising enterocolitis share a common initiating aetiological factor (for example, a specific infection) that causes mucosal necrosis, and that various host factors may modify the presentation of disease, including the development of pneumatosis cystoides intestinalis. Evidence in favour of this hypothesis comes from the often epidemic presentation of cases.[1] Such clustering suggests that infection may play an important part, and outbreaks are usually terminated by strict control of cross infection. It also seems that during clusters of confirmed necrotising enterocolitis the incidence of unconfirmed cases also increases. Sherertz and Sarubbi[21] reported a small outbreak of necrotising enterocolitis associated with *Clostridium difficile* infection in the nursery; four cases were confirmed and one was suspected (with bloody faeces, abdominal distension but no pneumatosis cystoides intestinalis). Cashmore *et al*[22] reported a larger outbreak in which 11 cases were confirmed and nine suspected during a four week period. In six clusters reported in the United Kingdom study in 1981–82, 11 of 24 cases were not confirmed radiologically, but this proportion was not significantly different from the 21 out of 32 sporadic cases in those units.[1] These data suggest that suspected and confirmed necrotising enterocolitis may be different responses to the same initial stimulus.

The necrotising enterocolitis surveillance scheme was successful in clarifying the clinical presentation of necrotising enterocolitis, it highlighted the occurrence of outbreaks,[1] and has helped to elucidate factors associated with mortality. Furthermore, it provided the basis for a multicentre case control study that identified risk factors for necrotising enterocolitis.[23] The under reporting, however, prevented the calculation of incidence rates for necrotising enterocolitis for the United Kingdom, and prevented regional comparisons. Future incidence surveys of necrotising enterocolitis should adopt active surveillance methods[6] rather than depending upon the physicians to initiate the reporting.

We thank members of the BAPM and colleagues at CDSC for supporting this project.

References

[1] British Association for Perinatal Paediatrics and Public Health Laboratory Service Communicable Disease Surveillance Centre. Surveillance of necrotising enterocolitis, 1981–82. *Br Med J* 1983;**287**:824–6.

[2] Smalls M, Forbes JF. *Centile values of birthweight for gestational age in Scottish infants.* Glasgow: Social, Paediatric, and Obstetric Research Unit, University of Glasgow, 1983.

[3] Office of Population Censuses and Surveys. *Birthweight statistics 1981, 1982.* OPCS Monitor DH3 83/3, 1983.

[4] Centers for Disease Control. Reye's syndrome – United States 1985. *MMWR* 1986;**35**:66–8.

[5] Centers for Disease Control. Reye's syndrome – United States 1985. *MMWR* 1986;**35**:73–4.

[6] Hall S, Glickman M. The British Paediatric Surveillance Unit, *Arch Dis Child* 1988;**63**:344–6.

[7] Communicable Disease Surveillance Centre, Reye's syndrome surveillance scheme. Third summary report. *Br Med J* 1985;**291**: 329–30.

[8] Yu, VYH, Tudehope DI, Gill GJ. Neonatal necrotising enterocolitis: 1. clinical aspects. *Med J Aust* 1977;**1**:685–8.

[9] Wilson R, Kanto WP, McCarthy BJ, *et al.* Epidemiologic characteristics of necrotising enterocolitis: a population based study. *Am J Epidemiol* 1981;**114**:880–7.

[10] Schullinger JN, Mollitt DL, Vinocur CD, Santulli TV, Driscoll JM. Neonatal necrotising enterocolitis, survival, management and complications: a 25 year study. *Am J Dis Child* 1981;**135**: 612–4.

[11] Kliegman RM. Fanaroff AA. Neonatal necrotising enterocolitis: a nine-year experience. II. Outcome assessment. *Am J Dis Child* 1981;**135**:608–11.

[12] Boyle R, Nelson JS, Stonestreet BS, Peter G, Oh W. Alterations in stool flora resulting from oral kanamycin prophylaxis of necrotising enterocolitis. *J Pediatr* 1978;**93**:857–61.

[13] Kleigman RM. Neonatal necrotizing enterocolitis: implications for an infectious disease. *Pediatr Clin North Am* 1979;**26**: 327–44.

[14] Book LS, Overall JC Jr, Herbst JJ, Britt MR, Epstein E, Jung AL. Clustering of necrotizing enterocolitis: interruption by infection-control measures. *N Engl J Med* 1977;**297**:984–6.

[15] Dykes EH, Gilmour WH, Azmy AF. Prediction of outcome following necrotising enterocolitis in a neonatal surgical unit. *J Pediatr Surg* 1985;**20**:3–5.

[16] Kliegman RM, Fanaroff AA. Necrotizing enterocolitis. *N Engl J Med* 1984;**310**:1093–103.

[17] Dolan P, Azmy AF, Young DG, Ziervogel M. Necrotising enterocolitis: experience with 54 neonates. *Scott Med J* 1984;**29**: 166–70.

[18] Anonymous. Colitis in term babies. *Lancet* 1983;**i**:1083–4.

[19] Kliegman RM, Fanaroff AA. Neonatal necrotizing enterocolitis in the absence of pneumatosis intestinalis. *Am J Dis Child* 1982;**136**:618–20.

[20] Bell MJ, Ternberg JL, Feigin RD, *et al.* Neonatal necrotizing enterocolitis: therapeutic decisions based upon clinical staging. *Ann Surg* 1978;**187**:1–7.

[21] Sherertz RJ, Sarubbi FA. The prevalence of Clostridium difficile and toxin in a nursery population: a comparison between patients with necrotizing enterocolitis and an asymptomatic group. *J Pediatr* 1982;**100**:435–9.

[22] Cashmore WJ, Peter G, Lauermann H, Stonestreet BS, Oh W. Clostridia colonisation and clostridial toxin in neonatal necrotizing enterocolitis. *J Pediatr* 1981;**98**:308–11.

[23] Palmer SR, Thomas SJ, Cooke RWI, *et al.* Birthweight-specific risk factors for necrotising enterocolitis. *J Epidemiol Community Health* 1980;**41**:210–4.

Correspondence to Dr SR Palmer, Public Health Laboratory Service, Public Health Laboratory, University Hospital of Wales, Heath Park, Cardiff CF4 4XW.

Accepted 11 August 1988

Archives of Disease in Childhood, 1989, **64,** 395–406

Short reports

Immunoreactive trypsin in Shwachman's syndrome

J F B DOSSETOR,* H C SPRATT,† C J ROLLES,‡ C P CHAN SEEM,* AND A F HEELEY§

**The Queen Elizabeth Hospital, King's Lynn; †The General Hospital, St Helier, Jersey; ‡Southampton General Hospital; and §Peterborough District General Hospital*

SUMMARY We studied two infants with Shwachman's syndrome in whom the immunoreactive trypsin concentration was found to be abnormally low. Experience with several hundred assays for immunoreactive trypsin has not shown this low concentration. This finding is probably specific for pancreatic acinar deficiency at this age and strongly suggests Shwachman's syndrome.

Shwachman's syndrome consists of a failure of pancreatic development, in which the exocrine component of the gland is largely or completely replaced by fatty tissue. It is associated with other abnormalities: most commonly neutropenia and short stature.[1] Measurement of serum immunoreactive trypsin was performed in the investigation of two cases of Shwachman's syndrome and found to be undetectable.

Case reports

CASE 1

A boy, who had weighed 2600 g at birth, was referred at the age of 11 months with failure to thrive and a history of diarrhoea associated with visible greasy material in the stools. His mother dated the onset of symptoms to when he was changed to bottle feeding and solids at the age of 3½ months, but in retrospect she agreed that his stools had been foul smelling while he was breast fed. She said that he had an insatiable appetite.

Investigation showed a haemoglobin concentration of 123 g/l and white cell count of $9{\cdot}33\times10^9$/l, with neutrophils of 13%. A sweat test was negative on two occasions (sweat chloride concentration 8 mmol/l and 13 mmol/l) and a jejunal biopsy specimen was normal. Fat globules were visible on stool microscopy and the three day faecal fat excretion was 13·0 g/day. Faecal trypsin activity was absent. Serum immunoreactive trypsin was undetectable. Duodenal juice stimulated by pancreazymin showed very low activities for amylase and lipase and undetectable tryptic activity. Enterokinase deficiency was excluded.

The child was given pancreatic enzyme supplements at the age of 15 months, his stools became normal and he started to thrive. A computed tomogram under general anaesthetic at the age of 20 months showed the pancreas to be completely replaced by material of the density of fat. The most recent white cell count was $3{\cdot}69\times10^9$/l with neutrophils of 17%.

CASE 2

A boy, who weighed 3300 g at birth, had persistent feeding difficulties in the neonatal period and was first admitted to hospital at the age of 9 days. He was admitted three times in the first few weeks of life, and failed to thrive. Immunoreactive trypsin was undetectable in the peripheral blood. Initially his full blood count showed a white cell count of $13{\cdot}6\times10^9$/l, with neutrophils of 31%. Two sweat tests were negative (sodium 8 mmol/l and 10 mmol/l).

Further investigation at a later date showed nephrocalcinosis on ultrasound, though this was not visible on the plain radiograph. Also at this time a chest radiograph showed broadened rib ends (metaphyseal dyschondroplasia), though other bones were normal. Neutropenia was by now evident (white cell count $8{\cdot}2\times10^9$/l, neutrophils 3%) and serum immunoreactive trypsin was again undetectable. These findings led to the diagnosis of Shwachman's syndrome.

Pancreatic enzyme supplements were started and the stools became normal. Subsequently a pancreatic function test was performed, which confirmed exocrine pancreatic insufficiency. A final complication was the development of a renal stone causing obstruction to the right ureter. After removal this was found to be 90% calcium oxalate. The nephrocalcinosis and stone formation were thought to be due to excess oxalate absorption secondary to malabsorption.[2]

Discussion

Many of the associated abnormalities found in Shwachman's syndrome such as the neutropenia and poor growth are not necessarily present at the time of presentation so that the diagnosis may be clinically difficult.[1] A computed tomogram of the pancreas gives a characteristic appearance in Shwachman's syndrome.[3] As a general anaesthetic is needed to perform this in a young infant it is not a first line investigation. Equally the practical difficulties associated with a pancreatic function test in an infant make the latter usually available only in specialised centres.

Among 711 infants aged between 1 week and 1 year whose serum immunoreactive trypsin concentrations were measured in the course of investigation for possible cystic fibrosis, immunoreactive trypsin was undetectable (that is, less than 3 μg/l) in only the two patients described. The results obtained in this large cohort of infants, of whom 165 presented predominantly with failure to thrive, lead us to conclude that when immunoreactive trypsin is undetectable in serum the cause is most likely to be the pancreatic acinar hypoplasia of Shwachman's syndrome. The immunoreactive trypsin screening test for cystic fibrosis only detects high values and will not pick up these cases, for whom the serum immunoreactive trypsin must be measured.

In patients with chronic pancreatitis[4] and cystic fibrosis[5] subnormal or undetectable immunoreactive trypsin may occur when pancreatic insufficiency results in steatorrhoea. In cystic fibrosis, however, undetectable serum immunoreactive trypsin concentrations are unlikely to be found before the age of 2 years irrespective of the degree of pancreatic insufficiency,[6] and in any case cystic fibrosis would be excluded by the sweat test.

In the light of these two cases, therefore, we would suggest that measurement of immunoreactive trypsin be performed at an early stage in the investigation of suspected malabsorption. It is remotely possible that the chronic inflammation of cystic fibrosis could destroy all the glandular tissue in infancy; but this diagnosis can be excluded by the sweat test. Hence, if serum immunoreactive trypsin is undetectably low and the sweat test is negative the inference must be that acinar production of trypsin is not occurring. This immediately makes Shwachman's syndrome very likely as the other conditions in which acinar trypsin production does not occur are very much rarer than Shwachman's syndrome. The abnormally low immunoreactive trypsin, therefore, justifies computed tomography of the pancreas as the next step, and in most cases will obviate the need for pancreatic function tests.

We thank Dr D Grant, department of surgery, St George's Medical School, London, for the measurement of duodenal juice trypsin and enterokinase activities.

References

1. Aggett PJ, Cavanagh NPC, Matthew DJ, Pincott JR, Sutcliffe J, Harries JT. Shwachman's syndrome. A review of 21 cases. *Arch Dis Child* 1980;**55**:331–47.
2. Ogilvie D, McCollum JPK, Packer S, *et al.* Urinary outputs of oxalate, calcium and magnesium in children with intestinal disorders. Potential cause of renal calculi. *Arch Dis Child* 1976;**51**:790–5.
3. Robberecht E, Nachtegaele P, Van Rattinghe R, Afschrift M, Kunnen M, Verharren R. Pancreatic lipomatosis in the Schwachman-Diamond syndrome. *Pediatr Radiol* 1985;**15**: 348–9.
4. Jacobson DG, Curington C, Connery K, Toskes PP. Trypsin-like immunoreactivity as a test for pancreatic insufficiency. *N Engl J Med* 1984;**310**:1307–9.
5. Cleghorn G, Benjamin L, Corey M, Forstner G, Dati F, Durie P. Serum immunoreactive pancreatic lipase and cationic trypsinogen for the assessment of exocrine pancreatic function in older patients with cystic fibrosis. *Pediatrics* 1986;**77**:301–6.
6. Durie PR, Forstner GG, Gaskin KJ, *et al.* Age related alterations of immunoreactive pancreatic cationic trypsinogen in sera from cystic fibrosis patients with and without pancreatic insufficiency. *Pediatr Res* 1986;**20**:209–13.

Correspondence to Dr J F B Dossetor, The Queen Elizabeth Hospital, Gayton Road, Kings Lynn, Norfolk PE30 4ET.

Accepted 24 October 1988

Aetiology of Kawasaki disease

B A BANNISTER,* S EDWARDS,† AND G IBATA†

**Department of Infectious Diseases, Royal Free Hospital at Coppetts Wood Hospital, London and †Virology Department, Central Veterinary Laboratory, Weybridge, Surrey*

SUMMARY Thirteen serum samples from nine children with Kawasaki disease and 23 control samples gave negative results on screening for antibodies to hog cholera virus, border disease of sheep, bovine diarrhoea virus, and equine arteritis virus. The sera from two children with Kawasaki disease were cytotoxic; a possible link with cytotoxin from *Propionibacterium acnes* is considered.

Kawasaki disease is characterised by vasculitis and accompanying thrombocythaemia, and it usually affects young children. The tendency for cases to appear in clusters and for the occurrence of 'epidemic years' suggests an infectious aetiology.[1] Many of the clinical features of Kawasaki disease have been described in infectious vasculitic diseases of animals, including acute hog cholera (synonymous with swine fever) in pigs[2] and equine viral arteritis.[3] We therefore undertook a small study of children with Kawasaki disease to seek serological evidence of infection with the causal viruses of these conditions or with related viruses of ruminants.

Patients and methods

Recent cases of Kawasaki disease were identified using the British Paediatric Surveillance Unit (BPSU) reporting system.[4] Reporting paediatricians were asked to provide sera from both the acute and convalescent stage of the disease from their cases. Control sera were obtained from age matched patients with a variety of acute infectious diseases. Thirteen sera from nine patients with Kawasaki disease and 23 control sera were examined.

Collected sera were coded, then frozen at −40°C until being examined 'blind'. Thawed sera were heat treated at 56°C for 30 minutes. Microtitre serum virus neutralisation tests were then carried out in duplicate using the following virus and cell culture combinations: (a) hog cholera virus (Baker A strain) with a porcine kidney cell line (PK 15); (b) an antigenically distinct isolate of hog cholera virus (1987) with PK 15; (c) border disease virus of sheep with bovine turbinate cells; (d) bovine viral diarrhoea virus with bovine turbinate cells; and (e) equine arteritis virus with a rabbit kidney cell line (RK 13).

All five viruses are classified as non-arthropod borne togaviridae, the first four in the genus pestivirus and the last as arterivirus. Virus growth in systems (d) and (e) was detected by cytopathic effect and in (a), (b), and (c) by the neutralising peroxidase linked assay of Holm Jensen to determine the 50% neutralisation end points.[5]

Results

The mean age of the nine cases was 3·3 years (range 1 to 9 years) and of the 23 controls 3·3 years (range 11 months to 9 years). No neutralisation effect was shown with sera from either the children with Kawasaki disease or the controls.

Two of the sera were cytotoxic to a dilution of 1:10—one from a boy aged 1 and the other from a girl aged 6 years. Both these samples were from convalescent patients who had fulfilled the BPSU criteria for Kawasaki disease. This is of some interest as recent work from Japan has suggested that lymph nodes from patients with Kawasaki disease may be infected with a strain of *Propionibacterium acnes* that produces a cytopathogenic substance.[6] Some children with Kawasaki disease have persisting high titres of antibodies to this substance; could our two patients have persisting cytotoxin in their circulation? Unfortunately, no further serum is available from either patient.

Discussion

This small study suggests that there is no direct relationship between Kawasaki disease of children and viral vasculitis diseases of farm animals. The cytotoxicity found in serum samples from two patients convalescing from Kawasaki disease, but not in samples from controls, may be relevant and deserves further study.

Sera from patients with Kawasaki disease were kindly submitted for test by paediatricians at the following hospitals: Airedale General Hospital; Booth Hall Children's Hospital; Bristol Hospitals; Lincoln Hospitals; National Children's Hospital, Dublin; Royal Gwent Hospitals; Saint Mary's Hospital, Newport, Isle of Wight; Scarborough General Hospital; and Glan Clwyd Hospital, Rhyl. We are grateful to G Wibberley for the equine arteritis tests.

References

[1] Rowley AH, Shulman ST. The search for the aetiology of Kawasaki disease. *Pediatr Infect Dis* 1987;6:506–8.

[2] Trautwein G. Pathology and pathogenesis of the disease. In: Liess B, ed. *Classical swine fever and related viral infections.* Dordrecht: Martinus Nijhoff, 1988:27–54.
[3] Timoney PJ, McCollum WH. Equine viral arteritis. *Canadian Veterinary Journal* 1987;**28**:693–5.
[4] Hall SM, Glickman M. The British paediatric surveillance unit. *Arch Dis Child* 1988;**63**:344–6.
[5] Holm Jensen M. Detection of antibodies against hog cholera virus and bovine viral diarrhoea in porcine serum. *Acta Vet Scand* 1981;**22**:85–98.
[6] Tomita S, Kato H, Fujimoto T, Inoue O, Koga Y, Kuriya N. Cytopathogenic protein infiltrates from cultures of Propionibacterium acnes isolated from patients with Kawasaki disease. *Br Med J* 1987;**295**:1229–32.

Correspondence to Dr B A Bannister, Department of Infectious Diseases, The Royal Free Hospital at Coppetts Wood Hospital, Coppetts Wood, Muswell Hill, London N10 1JN.

Accepted 11 October 1988

Kawasaki disease in siblings

M HEWITT,* L J SMITH,* H S JOFFE,† AND T L CHAMBERS*

**Children's Department, Southmead Hospital, and †Royal Hospital for Sick Children, Bristol*

SUMMARY We report a case of mucocutaneous lymph node syndrome, which was diagnosed in a 13 month old boy two years after the death of his sister from the same disease.

The aetiology of mucocutaneous lymph node syndrome, or Kawasaki disease, remains elusive, although it was first reported in 1967.[1] Environmental, genetic, and infective causes have all been postulated. We describe the non-contemporaneous occurrence of the disease in two children within the same family.

Case reports

CASE 1

In April 1983 a 6 month old girl was admitted for investigation of a prolonged fever. She had a two week history of ill health including coryzal symptoms, cervical lymphadenopathy, mild conjunctivitis, and a macular rash on her trunk. There had been no contact with infectious disease or travel abroad. Results of investigations are shown in the table.

On day 28 of her admission she developed mucousy diarrhoea and adenovirus type 5 was isolated from the stool. An adenovirus titre before this was negative but subsequently there was a significant rise to a titre of 64.

Her clinical condition deteriorated and nine days later she had a cardiac arrest. Resuscitation was successful and subsequent examination showed cardiac failure and gross cardiomegaly. A diagnosis of viral myocarditis was made. Despite symptomatic treatment there was further deterioration and the child died seven weeks after admission.

Postmortem examination found widespread coronary artery aneurysms with antemortem thrombi and extensive infarction. There was no evidence of pericarditis or myocarditis. The final diagnosis was therefore mucocutaneous lymph node syndrome.

CASE 2

A boy, born to the same parents two years after the death of his sister (case 1), was well until 13 months of age. He was seen with coryza, prolonged fever, cervical lymphadenopathy, conjunctivitis, and a macular rash over the trunk. Results of investigations are shown in the table. Echocardiography showed an area of echodensity at the origin of the

Table *Results of investigations*

Investigation	*Case 1*	*Case 2*
Haemoglobin (g/l)	100	113
White cell count ($\times 10^9$ g/l)	16·8	15·3
Neutrophil (%)	60	54
Lymphocytes (%)	29	44
Platelets ($\times 10^9$/l)	414	430
Erythrocyte sedimentation rate (mm in first hour)	116	66
Alanine aminotransferase (IU/l)*	264	30
Blood cultures	Negative	Negative
Complement fixation test:		
Respiratory syncytial virus	Negative	Negative
Adenovirus	Positive	Negative
Mycoplasma	Negative	Negative
Herpes simplex	Negative	Negative
Measles	Negative	—
Rubella	Negative	—
Neutralisation test:		
Coxsackie B	Negative	—
Paul-Bunnell	Negative	Negative
Throat swab	Negative	Negative

*Normal range 0–45 IU/l.

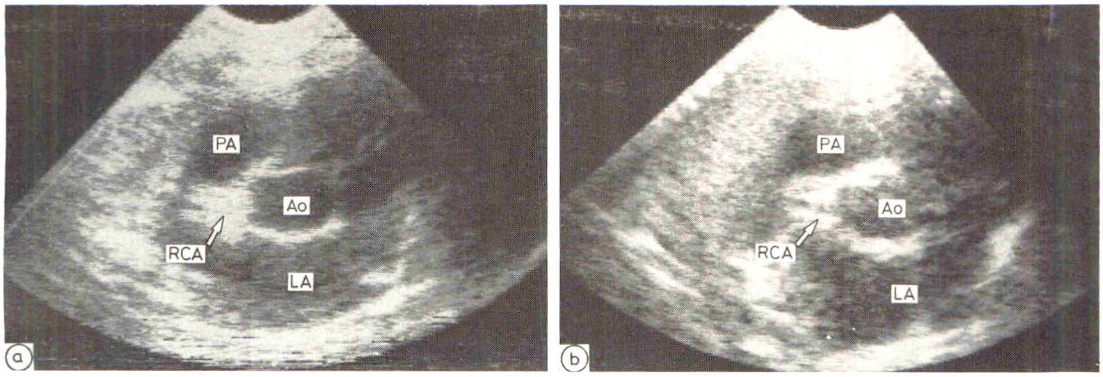


Figure *Echocardiogram of case 2 (a) showing cross sectional view of aortic root at presentation and thickening at the origin of the right coronary artery (RCA); (b) showing cross sectional view of aortic root at six months with partial resolution of the thickening at the origin of the right coronary artery. AO, aortic root; LA, left atrium, PA, pulmonary artery.*

right coronary artery (figure (a)), which was consistent with an inflammatory process. No aneurysms were found.

A diagnosis of mucocutaneous lymph node syndrome was therefore made and the child successfully treated with aspirin and gammaglobulin. Follow up echocardiography at six months showed partial resolution of the echodense area but there remained a residual thickening of the coronary artery walls (figure (b)).

Investigation of the parents and the other sibling was not undertaken.

Discussion

There have been previous case reports of siblings and twins with mucocutaneous lymph node syndrome but these have all occurred at the same time and thus lent support to the infectious aetiology.[2] Data on genetic factors such as HLA similarities have been inconsistent despite some evidence of association with linkage between HLA-A2, B44, and CW5 antigens.[3] A Japanese twin study failed to find any evidence of an excess of cases associated with genetic HLA identity.[4] The possibility of an environmental trigger—microbial or toxin mediated—precipitating an immune cascade and causing the release of platelet derived mediators in genetically predisposed individuals seems the most attractive hypothesis. Our case lends clinical support to this suggestion.

We thank the late Dr CR Tribe for his histopathological opinions on case 1.

References

[1] Kawasaki T, Kousaki F. Febrile oculo-oro-cutaneo-acro-desquamatous syndrome with or without acute non-superative cervical lymphadenitis in infancy and childhood. *Japanese Journal of Allergy* 1967;**16:**178–222.
[2] Lyen KR, Brook CDG. Mucocutaneous lymph node syndrome in two siblings. *Br Med J* 1978;**i:**1187–8.
[3] Kastow RA, Bailowitz A, Lin FYC, *et al.* Association of epidemic Kawasaki syndrome with the HLA A2, B44, CW5 antigen combination. *Arthritis Rheum* 1985;**28:**938.
[4] Harada F, Sada M, Karmya T, *et al.* Genetic analysis of Kawasaki syndrome. *Am J Hum Genet* 1986;**39:**537–9.

Correspondence to Dr M Hewitt, Institute of Child Health, Bristol Children's Hospital, Bristol.

Accepted 6 October 1988

400 *Archives of Disease in Childhood,* 1989, 64

Mildly anaemic toddlers respond to iron

Y A PARKS,* M A AUKETT,* J A MURRAY,† P H SCOTT,‡ AND B A WHARTON*

**Sorrento Maternity Hospital and Departments of †Haematology and ‡Biochemistry, Selly Oak Hospital, Birmingham*

SUMMARY Thirty eight children with a haemoglobin concentration of 106–110 g/l were given either oral iron (n=17) or placebo (n=21) for two months. The treated group achieved a significantly higher rise in haemoglobin concentration; in a quarter it was greater than 20 g/l. While those with the lower mean corpuscular volume and ferritin showed greater rises in haemoglobin these indices were of little value in predicting response in an individual child.

The definition of a normal haemoglobin concentration varies. It can be defined statistically as the mean plus or minus 2 standard deviations (SD), but the reference population studied may well include iron deficient children. Using these criteria a lower limit of normality is often set at 110 g/l.[1 2] Alternatively the positive response (a rise in haemoglobin of ≥10 g/l)[3] to a therapeutic trial of iron may be used to define iron deficiency anaemia. Other authors use a haemoglobin concentration less than 105 g/l as an indication for iron treatment.[4 5]

There exists therefore a group of children with haemoglobin concentrations of 106–110 g/l about whom opinions vary. Are children in this group anaemic and in need of iron treatment or can additional investigations define those in need of iron? A response to iron treatment is the gold standard' indicator of iron deficiency and it has been used in this investigation.

Subjects and methods

In a previous study we identified a group of 17–19 month old toddlers with a haemoglobin of 110 g/l or less (97 infants, 26% of screened population).[6] These anaemic children were randomly allocated to receive 10 ml of a mixture providing either 24 mg iron (as ferrous sulphate) plus 10 mg vitamin C daily or 10 mg vitamin C alone daily. Allocation was double blind using consecutively numbered bottles. After two months the children were reassessed.

Within this group of anaemic children 38 had a haemoglobin of 106–110 g/l. We have further analysed the results of other measurements of iron deficiency, and the response to iron in this group, because they are those children in whom the diagnosis of anaemia and iron deficiency is controversial. Seventeen children (12 boys and five girls, 15 Asians) received iron plus vitamin C, and 21 children (12 boys and nine girls, 19 Asians) received vitamin C alone. The social and anthropometric details of the two groups were similar.

The haematological and biochemical methods used were those described previously.[6] Thalassaemia was excluded by haemoglobin A2 and F determinations. Statistical analysis was by Fisher's exact test, Pearsons coefficient of correlation, and the paired *t* test as appropriate.

Results

EFFECT OF TREATMENT ON HAEMATOLOGICAL MEASUREMENTS (TABLE)

The mean rise in haemoglobin concentration in the treatment group was significantly higher than in the placebo group (17·7 g/l compared with 3·2 g/l, $p<0\cdot001$). The increase in haemoglobin was signifi-

Table 1 *Haematological values before and after treatment (mean (SD))*

	Group			
	Iron plus vitamin C (n=17)		*Vitamin C alone (n=21)*	
	Before	*After*	*Before*	*After*
Haemoglobin (g/l)	108 (1·0)	126 6·0)***	108 (1·0)	111 (8·0)
Mean corpuscular volume (fl)	64·8 (5·4)	69·3 (3·9)***	64·0 (5·8)	64·8 (6·6)
Mean corpuscular haemoglobin (pg)	21·3 (2·0)	23·1 (1·9)***	21·0 (2·3)	21·3 (2·5)
Serum iron (μmol/l)	10·4 (5·4)	15·7 (8·2)	10·0 (4·6)	9·7 (4·3)
Transferrin saturation (%)	8·7 (4·8)	16·8 (10·4)*	9·2 (7·7)	10·1 (11·7)
Ferritin (μg/l)	8·3 (4·8)	14·8 (9·5)**	9·2 (4·6)	9·9 (5·5)

Significant rise with treatment: *$p<0\cdot02$, **$p<0\cdot01$, ***$p<0\cdot001$ by paired *t* test.

cantly correlated with the increase in mean corpuscular volume ($r=0{\cdot}69$, $p<0{\cdot}01$), mean corpuscular haemoglobin ($r=0{\cdot}64$, $p<0{\cdot}01$), transferrin saturation ($r=0{\cdot}53$, $p<0{\cdot}05$), but not with change in iron ($r=0{\cdot}45$, $p=0{\cdot}09$) and ferritin concentrations ($r=-0{\cdot}12$, $p=0{\cdot}68$). All except one child in the treatment group achieved a haemoglobin rise of 10 g/l or more (that is, a significant rise according to criteria of Dallman *et al*[3]) compared with only five of the placebo group ($p<0{\cdot}01$).

PREDICTION OF RESPONSE TO IRON

This was examined in two ways: (1) the rise in haemoglobin was negatively correlated with the original haemoglobin concentration ($r=-0{\cdot}59$, $p<0{\cdot}02$), mean corpuscular volume ($r=-0{\cdot}48$, $p<0{\cdot}05$), and ferritin concentration ($r=-0{\cdot}51$, $p<0{\cdot}05$). The rise was not related to the original iron or mean corpuscular haemoglobin concentrations or the transferrin saturation. (2) Although a haemoglobin rise of more than 10 g/l has been accepted as a significant rise[3] we looked for a more stringent criterion. One child in the placebo group had a haemoglobin rise as high as 21 g/l, which could be regarded as the maximum possible change without treatment, four (24%) of the treated children achieved a haemoglobin rise greater than 21 g/l ($p=0{\cdot}03$ Fisher's exact test). These four children could therefore be defined as responders and the remaining 13 as limited responders. Comparison of the other haematological indices (figure) was not helpful in predicting response in an individual child. The responders all had a mean corpuscular volume and a ferritin concentration less than the means for limited responders.

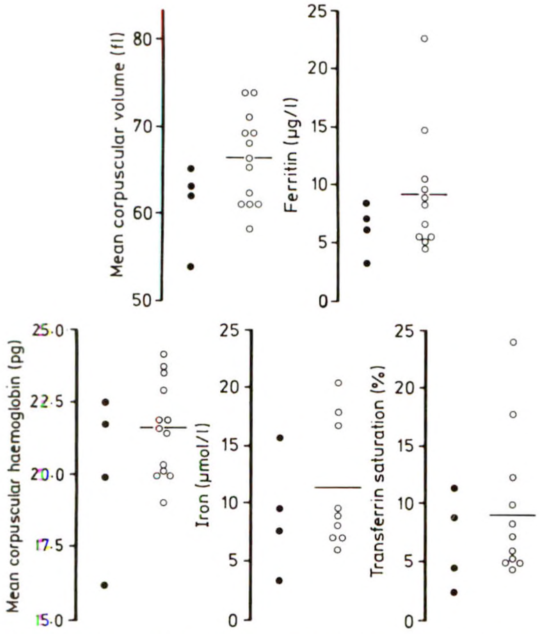


Figure *Comparison of haematological indices in subjects who responded to treatment with iron (●) with a rise in haemoglobin concentration of >21 g/l and those who had a limited response (○) with a rise in haemoglobin concentration of ≤21 g/l.*

Discussion

In this study we have shown that even if a child's haemoglobin concentration is 106–110 g/l treatment results in a substantial rise in mean haemoglobin. All except one child showed a rise of >10 g/l and even using the more stringent criterion of a rise of >21 g/l, 24% of the group showed this response. We have shown previously that a rise of 20 g/l is associated with a significant improvement in psychomotor development.[6]

Although overall the children with low original values for mean corpuscular volume and ferritin concentration showed the larger rises in haemoglobin, consideration of these measurements was of little value in predicting response to iron in an individual child.

Therefore in our opinion unless there is a clear contraindication or a clear suspicion of some other cause of the anaemia—for example, macrocytosis or polychromasia—all these children should be treated and their response monitored. It may be that some children with a haemoglobin concentration greater than 110 g/l would also show a rise in haemoglobin after iron treatment despite their not being anaemic according to the criteria of the World Health Organisation,[2] but this possibility was not examined in this paper.

References

[1] Dallman PR, Siimes MA. Percentile curves for haemoglobin and red cell volume in infancy and childhood. *J Pediatr* 1979;**94:** 26–31.

[2] World Health Organisation. Nutritional anaemias. *WHO Tech Rep Ser* 1972:No 503.

[3] Dallman PR, Reeves JD, Driggers DA, Lo EYT. Diagnosis of iron deficiency: the limitations of laboratory tests in predicting response to iron treatment in 1 year old infants. *J Pediatr* 1981; **98:**376–81.

[4] Lozoff B, Brittenham GM, Viteri FE, Wold AW, Urrutia JJ. The effects of short term iron therapy on developmental deficits in iron deficient anemic infants. *J Pediatr* 1982;**100:**351–7.

[5] Oski FA, Honig AS. The effects of therapy on developmental scores of iron deficient infants. *J Pediatr* 1978;**92:**21–5.

[6] Aukett MA, Parks YA, Scott PH, Wharton BA. Treatment with iron increases weight gain and psychomotor development. *Arch Dis Child* 1986;**61:**849–57.

Correspondence to Dr Y A Parks, Community Health, 41 Old Dover Road, Canterbury, Kent CT1 3HJ.

Accepted 21 September 1988

402 *Archives of Disease in Childhood,* 1989, **64**

Pseudocardiomyopathy secondary to chronic incessant supraventricular tachycardia

G GLADMAN, J L WILKINSON, AND G EVANS-JONES

Countess of Chester Hospital, Chester

SUMMARY A teenager with left ventricular dysfunction complicating chronic incessant supraventricular tachycardia is described. He was unusual in his delayed presentation to hospital, despite having come to medical attention several years previously, and he showed an excellent response to flecainide.

Chronic atrial tachycardia has previously been regarded as a benign process without any adverse myocardial sequelae. Subsequent investigators have established a relationship between incessant tachycardia and significant left ventricular dysfunction that presents clinically as a cardiomyopathy and we report such a case.[1 2]

Case report

A 6 year old boy was found by his family doctor to have a resting heart rate between 150–170 beats/minute. The general practitioner performed a 'rhythm strip' electrocardiogram at the time (January 1979) which confirmed the child's tachycardia (fig 1a), but as the child was asymptomatic no further action was taken.

Seven years later he was again found to have a tachycardia and was referred to the paediatric outpatient department. On questioning in the outpatient clinic it was evident that he was unaware of his fast heart rate and had been participating in normal physical activities. His only symptom was of feeling faint if he stood or knelt for any length of time.

On examination he had a resting pulse rate of 148 beats/minute and a poor pulse volume. There was clinical evidence of left ventricular enlargement, but no murmurs or gallop rhythm.

Electrocardiography performed at this time (May 1986) showed ectopic atrial tachycardia with evidence of left ventricular hypertrophy (fig 1b). Chest radiography showed appreciable left ventricular hypertrophy (fig 2a) and 24 hour electrocardiograms on two occasions showed the presence of an almost incessant afrial tachycardia with the occasional short break into sinus rhythm (mainly during sleep). An echocardiogram confirmed the presence of a dilated left ventricle, with significantly impaired contractility. His full blood count, erythrocyte sedimentation rate, and thyroid function tests were normal.

Treatment was initiated with the antiarrhythmic drug flecainide on a dosage of 50 mg twice a day; this was subsequently increased to 100 mg twice a day. This drug was well tolerated and provided consistently acceptable serum drug concentrations.

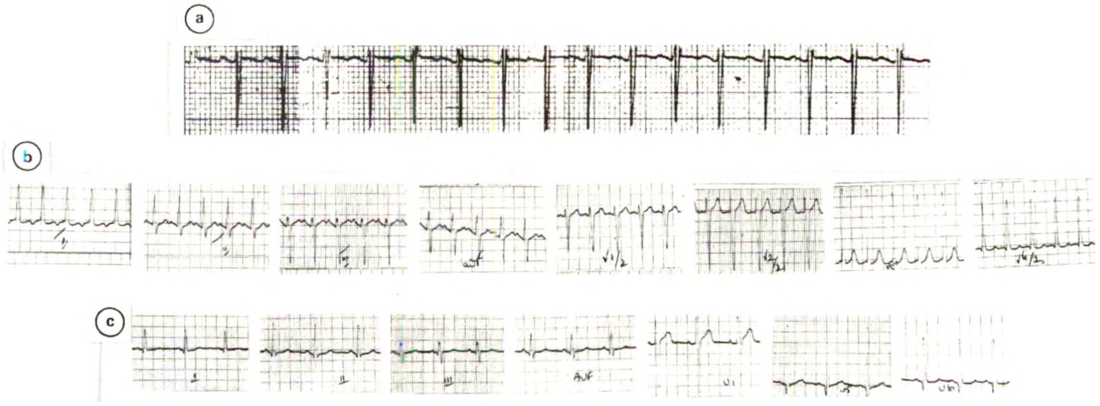


Fig 1 *Electrocardiography performed on the patient (a) in 1979, age 6; (b) in 1986, age 13; and (c) in 1987, age 14.*

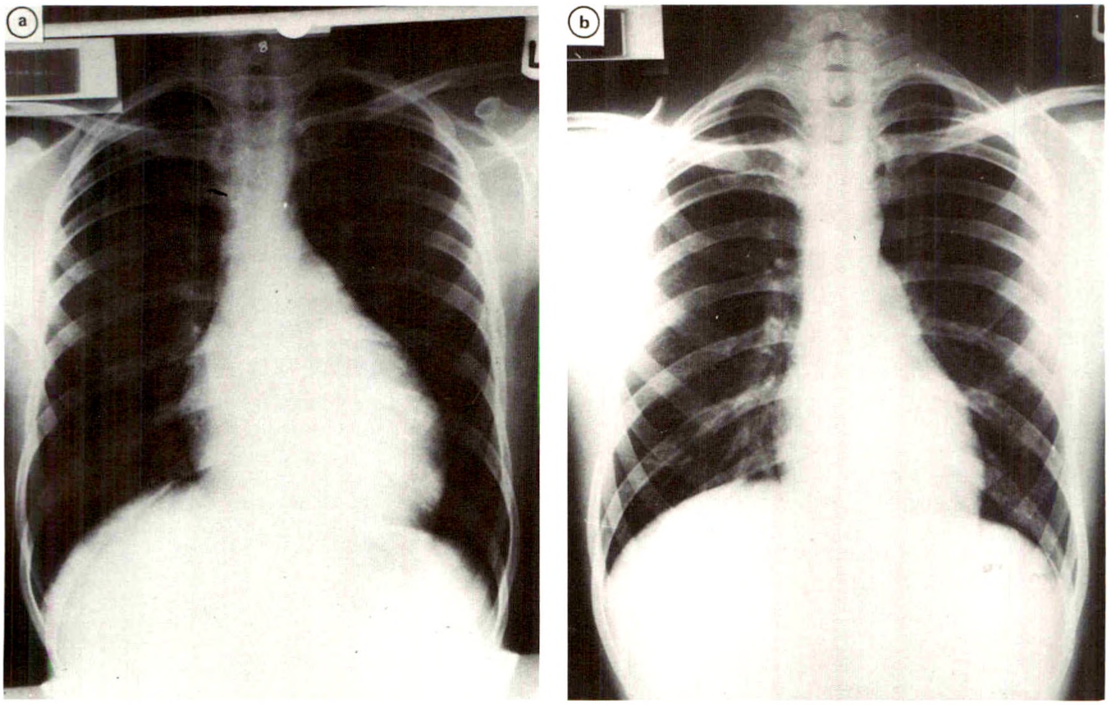


Fig 2 *Chest radiographs taken on the patient (a) in May 1986, age 13 (before treatment) and (b) after 18 months treatment with flecainide.*

Six months after commencing treatment he developed a fluctuating rash associated with exercise, anxiety, and heat. His full blood count and liver function tests were normal. A dermatological diagnosis of 'cholinergic urticaria' was made and treatment with an antihistamine was effective. The relationship between the rash and flecainide treatment was uncertain.

In the 18 months since drug treatment was commenced a considerable improvement in cardiac function has been noted: his electrocardiogram showed great improvement (fig 1c), a chest radiograph showed a return to normal (fig 2b), and a recent 24 hour electrocardiogram showed no evidence of tachycardia.

Discussion

The long history, normal exercise tolerance, and failure to show any underlying myocardial disease supports the hypothesis that this young man's poor left ventricular function was the result of his chronically uncontrolled tachycardia.

Electrophysiological studies have suggested that supraventricular tachycardias are the result of either an ectopic focus in the atria or A–V junction triggering abnormal impulses (automaticity) or due to the re-entry of conducted impulses, which may occur at the sinoatrial node; intra-atrial level; the atrioventricular node, or through anomalous atrioventricular connections.

Of these mechanisms, chronic persistent supraventricular tachycardias appear to result from either: (1) an automatic ectopic focus in the atrium (characterised on electrocardiography by 'P waves', of similar size and shape during the tachycardia, but morphologically different from the 'P waves' of sinus rhythm, together with a P–R interval that is variable but is always within normal limits and a narrow 'QRS' complex). (2) An automatic junctional ectopic focus (characterised on electrocardiography by 'P waves' frequently negative in leads II, III and aVF, and often following the 'QRS' complex). (3) A–V node re-entry, either of the 'slow-fast' form ('P waves', if seen, are inverted in leads II, III and aVF, the P–R interval is prolonged and the R–P interval is shortened) or of the 'fast-slow' form (again typified by a superior P wave axis but with a shortened P–R interval and a prolonged R–P interval). (4) A concealed lateral anomalous A–V pathway (with an apparently normal electrocardiogram when the patient is in sinus rhythm, differentiating this accessory pathway from the manifest anomalous pathway of the Wolff-Parkinson-White syndrome or the A–V node bypass of the Lown-Ganong-Levine syndrome).

In the absence of electrophysiological studies, the data available support the diagnosis of an ectopic atrial tachycardia in this young man.

The regression of a dilated cardiomyopathy picture is well reported after surgical treatment,[2] and more recently, following catheter ablation techniques.[3] Flecainide is increasingly being used for the management of supraventricular tachycardias and this case provides further evidence of its efficacy.[4 5]

This case is noteworthy, firstly because of the relatively low ventricular rate, and secondly because it provides clear evidence that the presence of left ventricular dysfunction is not always due to primary myocardial disease, but may be secondary to chronic tachycardia—in this case, incessant ectopic atrial tachycardia. As such, it is potentially reversible with specific antiarrhythmic drugs such as flecainide—hence the term 'pseudocardiomyopathy'.

References

[1] Gallagher JJ. Tachycardia and cardiomyopathy: chicken-egg dilemma revisited. *J Am Coll Cardiol* 1985;**6:**1172–3.

[2] Bertil Olsson S, Blomström P, Sabel KG, William Olsson G. Incessant ectopic atrial tachycardia: successful surgical treatment with regression of dilated cardiomyopathy picture. *Am J Cardiol* 1984;**53:**1465–6.

[3] Gillette PC. Treatment of atrial automatic tachycardia by ablation procedures. *J Am Coll Cardiol* 1985;**6:**405–9.

[4] Creamer JE, Nathan AW, Camm AJ. Successful treatment of atrial tachycardia with flecainide acetate. *Br Heart J* 1985;**53:** 164–6.

[5] Till JA, Rowland E, Shinebourne EA, Ward DE. Treatment of refractory supraventricular arrhythmias with flecainide acetate. *Arch Dis Child* 1987;**62:**247–52.

Correspondence to Dr G Gladman, Neonatal Medical Unit, St Mary's Hospital, Whitworth Park, Manchester M13 0JH.

Accepted 21 September 1988

Chronic neonatal Coxsackie myocarditis

A GOREN,* M KAPLAN,* J GLASER,† AND M ISACSOHN‡

*Departments of *Neonatology, †Pediatric Cardiology, and ‡Infectious Disesase Unit, Shaare Zedek Medical Center, The Hebrew University-Hadassah Medical School, Jerusalem, Israel*

SUMMARY A baby girl, with a birth weight of 2540 g, developed myocarditis with gross, permanent myocardial calcification. The clinical course was progressively downhill, and she died at 14 months of age. Neutralisation antibody to Coxsackie virus group B1 rose from 1:80 after delivery to 1:1280 at age 5 months. The protracted course of this infant's disease represents a new clinical form of fatal neonatal Coxsackie virus group B infection.

The clinical spectrum of neonatal infection with Coxsackie virus group B ranges from a mild, non-specific febrile illness to its severe, and often fatal, manifestation as myocarditis.[1 2]

We report a newborn girl with proved Coxsackie virus group B1 disease who had an unusually protracted course with chronic cardiac dysfunction, permanent myocardial calcification, and severe failure to thrive.

Case report

A girl, weighing 2540 g, was delivered at 36 weeks' gestation by caesarean section because of maternal fever, accompanied by dry cough and diarrhoea, and hypertension. The mother did not have a rash. Transient respiratory distress in the child was followed by the appearance of fever on the 4th day of life. A systolic heart murmur and a third heart sound became audible; subsequently there were numerous runs of supraventricular tachycardia and development of congestive cardiac failure. The cerebrospinal fluid contained leucocytes at a concentration of 200×10^6/l, the protein concentration was 1·4 g/l, and glucose 3·1 mmol/l. Serum glucose concentration was 4·1 mmol/l. Cultures of blood, urine, and cerebrospinal fluid were negative for bacterial growth. Despite ventilatory support and treatment with digoxin, diuretics, corticosteroids, and verapamil, the clinical condition did not improve and the arrhythmia persisted for many weeks.

Virological investigation showed neutralisation antibody to Coxsackie virus group B1 at 1:80 in the immediate neonatal period; this increased to 1:1280 at age 5 months. The virus could not be isolated from the stool or throat of either the mother or child.

From the 14th day of life echocardiographically distinguishable, extremely echogenic areas became visible in the left ventricular myocardium and gradually increased in intensity (fig 1). These areas subsequently appeared radiologically (fig 2) and on computed tomography as dense calcifications, and had not been present in early echocardiograms and radiographs. Ejection fraction, determined by multigated angiography, was severely impaired: on day 52 the ejection fraction was <40%. Although this improved substantially, myocardial function was still abnormal, with ejection fraction 63%, on day 115. Cardiac catheterisation showed pulmonary hypertension but no structural abnormality. Although the infant could gradually be weaned off the ventilator, her general condition remained poor. The congestive cardiac failure could be only incompletely controlled. Bouts of fever for which no apparent cause could be determined recurred frequently. Despite adequate nutritional intake there was severe failure to thrive. The infant died at age 14 months. Permission for necropsy could not be obtained.

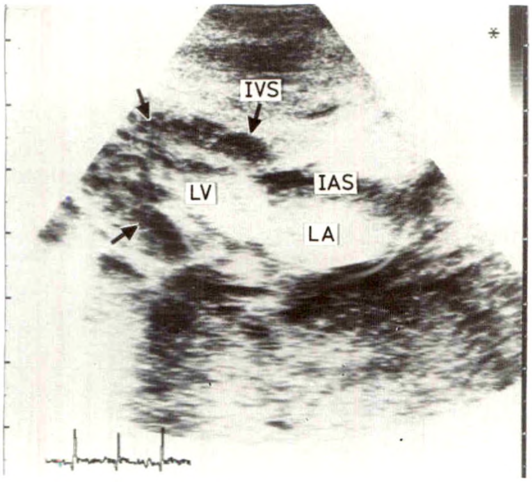


Fig 1 *Echocardiogram (subxiphoid four chamber view) at age 4 months. Note areas of extreme echogenicity in the left ventricular myocardium (arrows) probably due to calcification. IVS: interventricular septum; IAS: interatrial septum; LV: left ventricle; and LA: left atrium.*

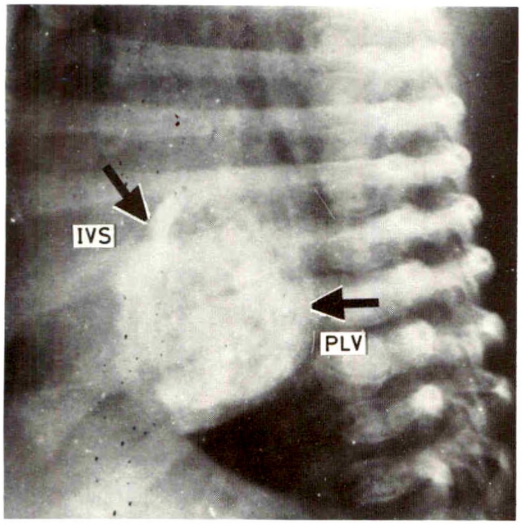


Fig 2 *Lateral radiograph of chest taken at age 6 weeks showing widespread calcification of the left ventricle (arrows). IVS, interventricular septum; PLV: posterior left ventricular wall.*

Discussion

Infants can became infected with Coxsackie virus group B by transplacental transmission, contact infection during birth, and by human contact after delivery.[1] Kaplan *et al* suggested that infection early in life is a significant factor leading to severe disease, and that in fatal cases the virus is transferred to the infant while in utero.[2] Thus the maternal febrile illness, early onset of the clinical signs, and the very severe course of the disease suggest that the infant we have described was infected transplacentally.

An unusual finding in our infant was the rapid development of severe myocardial calcification. We are aware of only one case in the literature, described by Barson *et al*,[3] of radiologically similar myocardial calcification associated with Coxsackie virus B4 infection. In contrast with our infant who had permanent calcification and subsequently died, their infant, however, recovered clinically, with complete resolution of the calcification by 7 months of age. Our experience shows that the calcification can be detected in its early stages by standard echocardiographic techniques, and should be actively sought out in infants with Coxsackie virus B myocarditis.

Despite an increasing titre of viral type specific antibodies in our infant, as the virus was not isolated from or localised to the cardiac tissue itself, a virus induced myocarditis could not be definitely determined.[4] Coxsackie virus group B, however, has been shown to cause histological myocardial calcification in both neonatal human[5] and murine tissue.[6] Thus it would appear that the myocardial calcification in our infant followed myocarditis caused by the Coxsackie B1 virus.

Reviewing their own eight proved, fatal cases and a further 33 fatal cases in the literature in which evidence of Coxsackie virus group B disease was documented, Kaplan *et al* determined that, except for one infant who died on day 90, death occurred within the neonatal period.[2] To our knowledge a clinical course of progressive myocarditis with myocardial calcification and severe cardiac dysfunction, resistance of the arrhythmia and congestive cardiac failure to medical treatment, and a prolonged downhill course with failure to thrive and death at age 14 months has not been previously described in association with fatal Coxsackie virus B infection of neonatal onset.

The authors thank Dr Rahel Hanscher of the Central Virology Laboratory of the Ministry of Health, Tel Hashomer, Israel, for determination of the antibody titres.

References

[1] Cherry JD. Coxsackie viruses B. In: Feigin RD, Cherry JD, eds. *Textbook of pediatric infectious diseases*. Philadelphia: WB Saunders, 1986:1322–69.

[2] Kaplan MH, Klein SW, McPhee J, Harper RG. Group B Coxsackievirus infections in infants younger than three months of age: a serious childhood illness. *Rev Infect Dis* 1983;**5**: 1019–32.

[3] Barson WJ, Craenen J, Hosier DN, Brawley RL, Hilty MD. Survival following myocarditis and myocardial calcification associated with infection by Coxsackie virus B-4. *Pediatrics* 1981;**68**:79–81.

[4] Reyes MP, Lerner AM. Coxsackievirus myocarditis – with special reference to acute and chronic effects. *Prog Cardiovasc Dis* 1985;**27**:373–94.

[5] Baker DA, Phillips CA. Maternal and neonatal infection with Coxsackievirus. *Obstet Gynecol* 1980;**55**(suppl):12–5.

[6] Reyes MP, Ho KL, Smith F, Lerner AM. A mouse model of dilated-type cardiomyopathy due to coxsackievirus B3. *J Infect Dis* 1981;**144**:232–6.

Correspondence to Dr M Kaplan, Department of Neonatology, Shaare Zedek Medical Center, PO Box 3235, Jerusalem 91031, Israel.

Accepted 1 September 1988

Archives of Disease in Childhood, 1989, **64,** 407–412

Regular review

Vesicoureteric reflux and renal scarring

R H R WHITE

The Children's Hospital, Birmingham

The urinary tract is often the site of bacterial infection during childhood. Population screening studies show a slight prevalence of boys during the neonatal period, followed by transition during infancy to a greater prevalence of girls, which progressively increases during the preschool years. Underlying structural abnormalities of the urinary tract are found in 30–50% of girls and in a somewhat higher proportion of boys with bacteriologically confirmed infection. Some of the abnormalities shown by routine radiological investigation after urinary tract infection—for example, partial duplication—are coincidental. Those abnormalities that play an aetiological role have in common distension and stasis as the underlying functional defect, and consist of (a) organic obstruction, (b) neuropathic bladder with functional obstruction, and (c) vesicoureteric reflux (VUR). The latter is by far the commonest abnormality and is the subject of this review.

During cystourethrography it is observed that VUR may occur during filling but is more likely to do so during voiding. Reflux occurring during filling is more likely when the ureter is grossly dilated and the vesicoureteric orifice is permanently open. It is possible, however, that it also occurs with a less severely incompetent vesicoureteric orifice if the patient also suffers from an unstable bladder, as detrusor contractions against a closed sphincter can generate appreciably higher intravesical pressures than those associated with voiding.[1] In a dilated system, a large volume of urine may be refluxed and will subsequently return to the bladder when the detrusor muscle relaxes after voiding, so that a residue is present continuously. It is this residue that almost certainly encourages bacterial colonisation of the bladder. Lesser degrees of VUR, in which radio-opaque contrast fluid is seen to enter an undilated ureter transiently, have correspondingly less clinical importance.

In both clinical practice and research it is necessary to evaluate the severity of VUR; several grading systems have been evolved,[2–5] differing essentially in their definitions of severe reflux. In Birmingham we have used a simple system[4] based on that of Rolleston *et al*[2]:

Grade 1—Reflux of contrast medium on filling or micturition which fails to reach the renal pelvis.
Grade 2—Reflux reaching the pelvis and calyces but without calyceal distension.
Grade 3—Reflux with distension of calyces.

While to include grotesquely dilated and tortuous ureters, often draining dysplastic kidneys, in grade 3 may be an oversimplification, the system elaborated by the International Reflux Study in Children goes to the opposite extreme of splitting severe VUR into grades 3–5 and further subdividing each of five grades into A, B, and C—a total of 15 subdivisions.[5] Such a complex system is more vulnerable to small errors of interpretation, and underlines the reality that reflux exhibits a continuous range of severity.

Reflux associated renal scarring

Although the possible role of VUR as a cause of urinary tract infection was first recognised 85 years ago,[6] it was the demonstration in 1960 by Hodson and Edwards of an association with renal scarring which renewed interest in the problem and generated the multidirectional research which is still gathering momentum more than quarter of a century later.[7] Since then the relationship between VUR and renal scarring has been extensively documented, particularly by Smellie *et al*,[3 8] and it is now a decade since we showed a significant correlation between the severity of VUR and the prevalence of renal scarring.[4] Because of this association, Bailey proposed the term *reflux nephropathy* which has now superseded the older term 'chronic pyelonephritis'.[9]

RADIOLOGICAL APPEARANCES

The radiological appearances of so called 'chronic atrophic pyelonephritis' were described in detail by

Hodson.[10] In health the renal parenchyma, as measured from the tip of each outermost papilla to the overlying renal outline, is thicker in the polar regions than in the middle third of the kidney; moreover the four polar measurements are approximately equal. The earliest sign of a focal scar is a reduction of cortical thickness. As the scar becomes more obvious, from contraction of fibrous tissue, the renal outline becomes indented while the underlying calyx becomes flattened ('blunted') and finally clubbed, from destruction of the papilla. It requires a very high standard of radiological preparation to detect small, early scars and, indeed, to exclude the presence of scarring. Focal scarring occurs more often in the upper than the lower poles, while bipolar and generalised scarring are both commoner than that which is confined to the middle zone; these observations are of relevance to the pathogenesis of reflux nephropathy (see below).

PATHOLOGY

Reflux nephropathy is primarily a tubulointerstitial disease. The histological changes were described in a now classical study of 100 necropsy cases of 'chronic pyelonephritis' by Weiss and Parker, who drew attention to the frequent origin of the condition during childhood.[11] The changes have been further elaborated by Heptinstall.[12] The interstitial tissue is infiltrated by chronic inflammatory cells, including lymphocytes and plasma cells, but in contracted scars these are less prominent and are replaced by collagen. The tubules show basement membrane thickening, epithelial cell atrophy, and collapse of the lumen, and eventually disappear. An additional and very characteristic change is dilatation of other tubules, with thin, atrophic epithelium and the inclusion of homogeneous eosinophilic casts—an appearance similar to normal thyroid tissue. Arteries and arterioles invariably show medial and intimal thickening when hypertension is present but may also do so in its absence. The glomerular changes are entirely secondary and are of two main kinds: (a) periglomerular fibrosis which is probably related to chronic intersititial inflammation; and (b) collapse or hyalinisation of the glomerular tuft, with or without concentric rings of collagen formed within the Bowman's capsule. The changes occurring in adjacent, unscarred renal tissue are essentially those of compensatory hypertrophy affecting both tubules and glomeruli, the latter often increasing in diameter by one third.[13] Other glomeruli may undergo segmental sclerosis, however, an aspect that will be considered later.

PATHOGENESIS

The two contrasting observations that 47% of all children with reflux, and even 21% of those with severe VUR, did not show reflux nephropathy, while a rare child with radiologically typical renal scarring did not have VUR,[4] suggest that the relationship between reflux and the nephropathy is not a simple one. The finding of scarring without VUR, usually in an older child, is easy to explain with the knowledge that reflux has a tendency to resolve spontaneously, given time.[3]

The demonstration of intrarenal reflux was a landmark in the understanding of VUR. Rolleston *et al* observed that renal scarring developed in precisely the same anatomical segment of the kidney as that in which intrarenal reflux had been shown radiologically.[14] Hodson *et al* confirmed these findings experimentally in pigs.[15] Ransley and Risdon showed that in human necropsy preparations from infants and young children some papillae were fused together to form compound structures in which papillary ducts opened perpendicularly on to a flat or concave surface, rather than tangentially on to the sides of conical structures.[16] Such compound papillae were found more often in the polar than mid-zone regions of the kidney—a distribution which coincides precisely with that of radiologically observed scars.[10] Here then was a mechanism whereby infected urine from the bladder could gain access to the renal parenchyma. Hodson *et al* succeeding in causing parenchymal scarring in refluxing pigs with sterile urine, but their model was one of chronic bladder neck obstruction.[15] Ransley and Risdon, however, were unable to reproduce their results and concluded that non-obstructive reflux nephropathy only developed in the presence of urinary tract infection.[17] In practice this is what we observe in humans.

In Hodson's experimental model high intravesical pressures were sustained through progressive compression of the urethra by a ring that was designed not to expand as the piglet grew.[15] This raised the question whether raised pressure could play a part in the aetiology of reflux nephropathy. In primary VUR there is no evidence of obstruction and high intravesical pressures are only likely in the presence of detrusor instability associated with dyssynergia. Taylor *et al* found that although a high proportion of both girls and boys with VUR also had detrusor instability, its presence or absence did not correlate with either the prevalence of reflux nephropathy[1] or the rate of resolution of reflux.[18]

It is of considerable interest that most reflux associated renal scars detected are already present when the patient is first investigated. In a retrospective survey involving 23 paediatric departments in the United Kingdom, Smellie *et al* were able to document only 87 new scars over a 22 year period.[19]

These developed at any age from infancy to 9 years but were rare after the seventh birthday. In a prospective therapeutic trial the Birmingham Reflux Study Group detected only 10 new scars among 161 children, the oldest being 7 years old.[20] This is relevant to the observation that intrarenal reflux has not been shown after the fifth birthday[14] and indicates that it is the youngest children who are most vulnerable to the consequences of VUR. In our prospective study we noted that 57% of infants with severe VUR already had reflux nephropathy at initial investigation.[20]

It has to be accepted that diffusely scarred, shrunken kidneys found in infants with hugely dilated, refluxing ureters probably represent dysplasia, although the precise aetiological role of sterile, intrauterine VUR is still unsettled.[21] Hereditary factors may also play a part in the anatomical malformations affecting the ureterovesical junction that permit reflux to occur.[22]

CLINICAL SIGNIFICANCE

In epidemiological surveys of schoolgirls aged 5–11 years, one third of those with covert bacteriuria were found to have VUR and one fifth reflux nephropathy.[23-25] Similarly, in a retrospective analysis of outpatients with urinary tract infection (from whom we excluded children with neuropathic bladder, obstructive uropathy, and congenital renal anomalies) we found that 52% of 104 children had VUR and that 23% of their kidneys were scarred.[4] It is noteworthy that all but one of the infants in this series had severe reflux, and that there were more boys than girls in this age group. From a total of more than 50 000 schoolgirls screened Hodson estimated the prevalence of reflux nephropathy to be one in 250 individuals.[26]

There is an increased risk of hypertension due to both unilateral and bilateral reflux nephropathy,[27] and of progression to chronic renal failure in the case of extensive bilateral disease. While there are as yet no reliable figures for the incidence of chronic renal failure based on prospective studies, preliminary figures suggest that this is around 5–6%.[20] Nevertheless, 'chronic pyelonephritis' accounted for 27% of children[28] and 21% of adults[29] entering renal replacement programmes in Europe, and reflux nephropathy was found to be the commonest single cause of chronic renal failure in a large childhood series.[30] Thus any effective method of preventing the development or extension of renal scarring might be expected to have an appreciable impact on the escalating costs of dialysis and transplantation.

Management of VUR

From the foregoing discussion we may conclude that human reflux nephropathy is a largely acquired lesion, dependent upon the coexistence of VUR, intrarenal reflux, and urinary tract infection. In our present state of knowledge intrarenal reflux is unalterable, and we are left with reflux and infection to treat. The main aims of treatment are firstly the relief of symptoms, which are mainly due to urinary tract infection and detrusor instability, and secondly the prevention or limitation of renal parenchymal damage.

SYMPTOMATIC TREATMENT

Symptomatic management has been fully discussed elsewhere and will merely be summarised here.[31 32] A notable finding in our prospective therapeutic trial was that children exposed to breakthrough urinary tract infection during the first two years' observation showed no higher incidence of progressive renal scarring or new scar formation than those unexposed.[33 34] Moreover, 82% of scars that progressed, and all 10 new ones that developed, were observed to do so during the first two years' treatment.[20] As the radiologically witnessed renal scar is the late result of parenchymal fibrous contraction[35] it is probable that all these changes were initiated before entry into the study. Although there is no doubt that carefully monitored chemoprophylaxis can reduce the incidence of bacteriuria,[36] these recent findings bring into question its long term value as a means of preventing progressive scarring. Compliance with treatment can never, in practice, be monitored with perfection, and in our study we showed breakthrough urinary tract infection in a quarter of the children who were nominally receiving chemoprophylaxis.[20] Hitherto many would have regarded the witholding of treatment in the presence of VUR and renal scarring as unethical, but these recent observations suggest the need for a controlled study in which chemotherapy is given only for symptomatic urinary tract infection. In the meantime our practice is to maintain chemoprophylaxis for a period of two years in children who are less than 5 years old at diagnosis, and in whom grade 2–3 VUR is present. The two most effective drugs are nitrofurantoin and trimethoprim, because the emergence of bacterial resistance against them is fortunately rare. Nitrofurantoin suspension is apt to cause nausea and sometimes vomiting, but older children can usually swallow 50 mg capsules of the drug. Either drug should be given as a single evening dose of 1–2 mg/kg/day.

Other aspects of medical management include the encouragement of a liberal fluid intake to create a bladder washout effect, and in girls with detrusor instability of sufficient intensity to cause diurnal incontinence a programme of voiding every two hours can be used.[31] [32] Double voiding, particularly at bedtime, can be employed to reduce the residual bladder urine volume that results from grossly dilated ureters and tends to encourage urinary tract infection. An important but poorly recognised feature of recurrent urinary tract infection and VUR is constipation.[32] The poor perineal muscular relaxation that accompanies detrusor instability impedes both bladder and rectal emptying, and careful abdominal palpation almost invariably shows a distended descending colon. Thus an essentia component of management is the introduction of a high fibre diet which, by increasing faecal bulk and softness, facilitates muscular relaxation and thereby helps to reduce residual urine.

Operative correction of VUR has a high technical success rate in experienced hands,[20] and this would seem to be a logical way of preventing infected urine from reaching the renal parenchyma. Claims of improved renal growth after ureteric reimplantation, however, were not supported by parallel observations in control patients treated medically.[37] Moreover, the possible benefits of reimplantation must be balanced against the tendency for reflux to resolve spontaneously over a long period.[3] [38]

In 1975 the Birmingham Reflux Study Group set up a prospective trial of operative compared with non-operative treatment of severe VUR. Children with grade 3 VUR were randomly allocated within three age groups (<1, 1–5, 6–14 years old at entry) and reinvestigated, functionally and radiologically, at intervals of two and five years from operation or from allocation to non-operative treatment. Altogether 161 children have been observed for two years and 104 of them for five years. The five year results[20] confirmed and extended those obtained after two years' observation.[33] [34] No significant differences were observed between treatment modes in the incidence of breakthrough urinary tract infection, renal excretory function and concentrating ability, renal growth, the progression of existing scars, or the development of new ones. The technical success rate of reimplantation was 98% whereas 51% of ureters treated non-operatively still showed grade 3 VUR after five years' chemoprophylaxis. When reflux was bilateral there was an increased tendency for it to persist. The long term effects of VUR persisting into adulthood remain to be evaluated; nevertheless its persistence did not adversely affect renal growth or increase the risks of scar progression.

Thus we have failed to show superiority for either mode of treatment; indeed the extremely poor growth of scarred kidneys in children aged more than 5 years at entry to the study questions whether any form of intervention is likely to be effective in older patients. In contrast, younger children showed evidence of catch up renal growth after two years' chemoprophylaxis, and are the ones who are more likely to benefit from treatment. Ransley and Risdon showed in refluxing piglets that irreversible renal scarring could develop within one week of introducing *Escherichia coli* into the bladder.[39] The high prevalence of scarring already present in our patients at entry to the study,[20] even in infants, suggests that this is also true of humans, and underlines the need for more prompt diagnosis and vigorous treatment of the *first* urinary tract infection. Although severe VUR may now be suspected antenatally from the ultrasonic appearance of the urinary tract,[40] cystourethrography is necessary postnatally to confirm the diagnosis. What is needed, and yet still eludes us, is a reliable and non-invasive method of diagnosing reflux in neonates.

Meanwhile the choice of treatment of VUR remains arbitrary and will depend on social factors that may influence compliance with prolonged chemotherapy, the availability of surgical skill, and perhaps parental preference. The endoscopic injection of Teflon under the bladder mucosa immediately below the affected ureteric orifice sounds a promising alternative to the conventional but more invasive surgical reimplantation procedure,[41] but has not yet been assessed prospectively in a controlled manner.

Prognosis

What does the future hold for patients with persistent reflux and those who have sustained renal damage? Little is known about the effects of persistent VUR in subjects with undamaged kidneys, although preliminary evidence suggests that their renal function is secure.[42] It can be speculated that those individuals who have not developed reflux nephropathy during childhood will never do so because their kidneys do not possess refluxing papillae. Patients with reflux nephropathy are at increased risk of hypertension,[27] although in our experience this is a rare complication of unilateral scarring. Patients with bilateral nephropathy may or may not show impaired renal function, depending upon the extent of the scarring.

Until recently we have argued that the future health of individuals in whom the scarring is confined to one kidney is secure, based on glomerular filtration measurements carried out during childhood.[31] There is increasing evidence, however, that a proportion of these patients sustain secondary changes of a progressive nature in the contralateral kidney. Persistent, heavy proteinuria is recognised as a sinister development in patients with reflux nephropathy,[43] and it is invariably present in those who progress to end stage renal failure.[44] Kincaid-Smith showed focal and segmental glomerulosclerosis in a high proportion of renal biopsy and nephrectomy specimens obtained from adult patients with reflux nephropathy and proteinuria, including some with normal or near normal renal function.[45] That they were present in the unscarred contralateral kidney in four patients with unilateral reflux nephropathy was a highly significant finding. In women with proteinuria, focal and segmental glomerulosclerosis, and raised plasma creatinine concentrations, the advent of either pregnancy or accelerated hypertension may lead to rapid deterioration of renal function.[46]

Ongoing research

Little is known about the early evolution of proteinuria in reflux nephropathy. Most of the patients investigated were adults, although similar glomerular lesions have been reported in a few children.[47 48] The introduction of more sensitive methods of determining protein concentration, however, has made observations on 'microproteinuria' possible. Bell *et al* recently showed significantly increased excretion rates of albumin and retinol binding protein in children with severe VUR and renal scarring, compared with those whose kidneys were unscarred.[49] Using the Coomassie blue dye binding method of measuring total protein concentration, which is both simple and cheap yet more sensitive than the biuret method at low concentrations, we first determined the normal range of protein:creatinine ratios in early morning urine samples obtained from 377 healthy subjects aged 3–19 years.[50] We then assessed proteinuria in children with VUR, finding no correlation with the degree of reflux but a trend towards increasing microproteinuria with increasingly severe renal scarring, and an inverse correlation with glomerular filtration rate as determined by slope clearance of ^{51}chromium edetic acid.[51]

These findings have prompted in depth studies of microproteinuria in reflux nephropathy in children. Our preliminary renal biopsy studies have confirmed that focal and segmental glomerulosclerosis accompanies proteinuria even of short duration and at below nephrotic levels. The lesion appears to originate in the parahilar region of the glomerulus. Additionally we have observed thickening and hyaline droplet infiltration of the hilar arterioles in unsclerosed glomeruli (M Morita, RHR White, F Raafat, unpublished observations). These changes are compatible with Brenner's finding that rats develop proteinuria and glomerular sclerosis after extensive renal ablation, if maintained on normal or high dietary protein intakes, and with his hypothesis that the changes are haemodynamically mediated.[52] Moreover, we have shown that experimental restriction of dietary protein intake in children with reflux nephropathy and proteinuria consistently leads to reduction of the urinary protein excretion rate (CM Taylor, JS Elises, E Buchanan, DJ Worthington, RHR White, MH Winterborn, unpublished observations). While it would be premature to conclude that dietary protein restriction is an effective form of preventive management, these early results have nevertheless encouraged us to pursue these investigations further.

The past quarter century has witnessed a wealth of significant contributions to the understanding of VUR and reflux nephropathy, in which the late Professor John Hodson had a prominent place from the start,[53] and yet it is apparent that there remains ahead of us a lifetime of research in this fascinating and important field of medicine.

This article is based on lectures given to the Philippine Society of Nephrology, Manila, on 26 March and at Keio University School of Medicine, Tokyo, on 17 May 1988, and is reproduced in modified form by courtesy of the *Philippine Journal of Nephrology*.

References

[1] Taylor CM, Corkery JJ, White RHR. Micturition symptoms and unstable bladder activity in girls with primary vesicoureteric reflux. *Br J Urol* 1982;**54:**494–8.

[2] Rolleston GL, Shannon FT, Utley WLF. Relationship of infantile vesicoureteric reflux to renal damage. *Br Med J* 1970;**i:**460–3.

[3] Smellie JM, Edwards D, Hunter N, Normand ICS, Prescod N. Vesicoureteric reflux and renal scarring. *Kidney Int* 1975;**8**(suppl 4):S65–72.

[4] Shah KJ, Robins DG, White RHR. Renal scarring and vesicoureteric reflux. *Arch Dis Child* 1978;**53:**210–7.

[5] Lebowitz RL, Olbing H, Parkkulainen KV, Smellie JM, Tamminen-Möbius TE. International system of radiographic grading of vesicoureteric reflux. *Pediatr Radiol* 1985;**15:**105–9.

[6] Sampson JA. Ascending renal infection with special reference to the reflux of urine from the bladder into the ureters as an aetiological factor in its causation and maintenance. *Bulletin of the Johns Hopkins Hospital* 1903;**14:**334–50.

[7] Hodson CJ, Edwards D. Chronic pyelonephritis and vesicoureteric reflux. *Clin Radiol* 1960;**11:**219–31.

[8] Smellie JM, Hodson CJ, Edwards D, Normand ICS. Clinical and radiological features of urinary tract infection in childhood. *Br Med J* 1964;**ii:**1222–6.

[9] Bailey RR. The relationship of vesico-ureteric reflux to urinary tract infection and chronic pyelonephritis—reflux nephropathy. *Clin Nephrol* 1973;**1:**132–41.

[10] Hodson CJ. The radiological contribution toward the diagnosis of chronic pyelonephritis. *Radiology* 1967;**88:**857–71.

[11] Weiss S, Parker F. Pyelonephritis: its relation to vascular lesions and to arterial hypertension. *Medicine (Baltimore)* 1939;**18:**221–315.

[12] Heptinstall RH. Pyelonephritis. II. Pathological features. *Pathology of the kidney.* Boston: Little, Brown, 1966:421–54.

[13] El-Khatib MT, Becker GJ, Kincaid-Smith P. Morphometric aspects of reflux nephropathy. *Kidney Int* 1987;**32**:261–5.

[14] Rolleston GL, Maling TMJ, Hodson CJ. Intrarenal reflux and the scarred kidney. *Arch Dis Child* 1974;**49**:531–9.

[15] Hodson CJ, Maling TMJ, McManamon PJ, Lewis MG. The pathogenesis of reflux nephropathy (chronic atrophic pyelonephritis). *Br J Radiol* 1975;**suppl 13**:1–26.

[16] Ransley PG, Risdon RA. Renal papillary morphology in infants and young children. *Urol Res* 1975;**3**:111–3.

[17] Ransley PG, Risdon RA. Reflux and renal scarring. *Br J Radiol* 1978;**suppl 14**:1–35.

[18] Taylor CM. Unstable bladder activity and the rate of resolution of vesico-ureteric reflux. In Hodson CJ, Heptinstall RH, eds. *Contributions to nephrology: reflux nephropathy update*. Basel: Karger, 1984:238–46.

[19] Smellie JM, Ransley PG, Normand ICS, Prescod N, Edwards D. Development of new renal scars: a collaborative study. *Br Med J* 1985;**290**:1957–60.

[20] Birmingham Reflux Study Group. Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux in children: five years' observation. *Br Med J* 1987;**295**:237–41.

[21] Risdon RA. The small scarred kidney of childhood: a congenital or an acquired lesion. *Pediatr Nephrol* 1987;**1**:632–7.

[22] De Vargas A, Evans K, Ransley P, *et al*. A family study of vesicoureteric reflux. *J Med Genet* 1978;**15**:85–96.

[23] Savage DCL, Wilson MI, McHardy M, Dewar DAE, Fee WM. Covert bacteriuria of childhood: a clinical and epidemiological study. *Arch Dis Child* 1973;**48**:8–20.

[24] McLachlan MSF, Meller ST, Verrier Jones ER, *et al*. Urinary tract in schoolgirls with covert bacteriuria. *Arch Dis Child* 1975;**50**:253–8.

[25] Edwards B, White RHR, Maxted H, Deverill I, White PA. Screening methods for covert bacteriuria in schoolgirls. *Br Med J* 1975;**ii**:463–7.

[26] Hodson J. Reflux nephropathy. *Med Clin North Am* 1978;**62**:1201–21.

[27] Wallace DMA, Rothwell DL, Williams DI. The long-term follow-up of surgically treated vesicoureteric reflux. *Br J Urol* 1978;**50**:479–84.

[28] Donckerwolcke RA, Chantler C, Brunner FP, *et al*. Combined report on regular dialysis and transplantation of children in Europe, 1977. In Robinson BHB, Hawkins JE, eds. *Proceedings of the European Dialysis and Transplant Association*. London: Pitman, 1978;**15**:77–114.

[29] Wing AJ, Brunner FP, Brynger HAO, *et al*. Combined report on regular dialysis and transplantation in Europe, 1977. In Robinson BHB, Hawkins JB, eds. *Proceedings of the European Dialysis and Transplant Association*. London: Pitman, 1978;**15**:2–76.

[30] Chantler C. Progressive loss of renal function In Holliday MA, Barratt TM, Vernier RL, eds. *Pediatric nephrology*. 2nd ed. Baltimore: Williams and Wilkins, 1987:773–93.

[31] White RHR, Taylor CM. The non-operative management of primary vesicoureteric reflux. In: Johnston JH, ed. *Management of vesicoureteric reflux*. Baltimore: Williams and Wilkins, 1984:117–36.

[32] White RHR. Management of urinary tract infection. *Arch Dis Child* 1987;**62**:421–7.

[33] Birmingham Reflux Study Group. Prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux: two years' observation in 96 children. *Br Med J* 1983;**287**:171–4.

[34] Birmingham Reflux Study Group. A prospective trial of operative versus non-operative treatment of severe vesicoureteric reflux: two years' observation in 96 children. In Hodson CJ, Heptinstall RH, eds. *Contributions to nephrology: reflux nephropathy update*. Basel:Karger, 1984:169–85.

[35] Scott JES. The role of surgery in the management of vesicoureteric reflux. *Kidney Int* 1975;**8(suppl 4)**:S73–80.

[36] Smellie JM, Gruneberg RN, Bantock HM, Prescod N. Prophylactic co-trimoxazole and trimethoprim in the management of urinary tract infection in children. *Pediatr Nephrol* 1988;**2**:12–7.

[37] McRae CU, Shannon FT, Utley WLF. Effect on renal growth of reimplantation of refluxing ureters. *Lancet* 1974;**i**:1310–2.

[38] Edwards D, Normand ICS, Prescod N, Smellie JM. Disappearance of vesicoureteric reflux during long-term prophylaxis of urinary tract infection. *Br Med J* 1977;**ii**:285–8.

[39] Ransley PG, Risdon RA. Reflux nephropathy: effects of antimicrobial therapy on the evolution of the early pyelonephritic scar. *Kidney Int* 1981;**20**:733–42.

[40] Watson AR, Readett D, Nelson CS, Kapila L, Mayell MJ. Dilemmas associated with antenatally detected urinary tract abnormalities. *Arch Dis Child* 1988;**63**:719–22.

[41] O'Donnell B, Puri P. Endoscopic correction of primary vesicoureteric reflux. *Br J Urol* 1986;**58**:601–4.

[42] Verrier Jones K, Asscher AW, Verrier Jones ER, Mattholie K, Leach K, Thomson GM. Glomerular filtration rate in schoolgirls with covert bacteriuria. *Br Med J* 1982;**285**:1307–10.

[43] Kincaid-Smith P, Becker G. Reflux nephropathy and chronic atrophic pyelonephritis: a review. *J Infect Dis* 1978;**138**:774–80.

[44] Bailey RR. End-stage reflux nephropathy. *Nephron* 1981;**27**:302–6.

[45] Kincaid-Smith P. Glomerular lesions in atrophic pyelonephritis and reflux nephropathy. *Kidney Int* 1975;**8(suppl 4)**:S81–83.

[46] Becker GJ, Ihle BU, Fairley KF, Bastos M, Kincaid-Smith P. Effect of pregnancy on moderate renal failure in reflux nephropathy. *Br Med J* 1986;**292**:796–8.

[47] Aladjem M, Schoeneman MJ, Bennett B, Levitt S, Spitzer A, Greifer I. Focal glomerulosclerosis with proteinuria and chronic interstitial nephritis. *NY State J Med* 1978;**78**:579–81.

[48] Bhathena DB, Weiss JM, Holland NH, *et al*. Focal and segmental glomerular sclerosis in reflux nephropathy. *Am J Med* 1980;**68**:886–92.

[49] Bell FG, Wilkin TJ, Atwell JD. Microproteinuria in children with vesicoureteric reflux. *Br J Urol* 1986;**58**:605–9.

[50] Elises JS, Griffiths PD, Hocking MD, Taylor CM, White RHR. Simplified quantification of urinary protein excretion in children. *Clin Nephrol* 1988;**30**:225–9.

[51] White RHR, Taylor CM, Elises JS, Griffiths PD. Proteinuria and reflux nephropathy. In: Walker RG, Kincaid-Smith P, eds. *Proceedings of the First CJ Hodson Symposium on Reflux Nephropathy*. Melbourne: Broughton Printing, 1987:15–20.

[52] Brenner BM. Nephrology forum. Hemodynamically mediated glomerular injury and the progressive nature of kidney disease. *Kidney Int* 1983;**23**:647–55.

[53] Smellie JM. John Hodson: an appreciation of his achievement and contributions to paediatric nephrology. *Pediatr Nephrol* 1987;**1**:563–5.

Correspondence to Professor R H R White, Department of Nephrology, The Children's Hospital, Ladywood Middleway, Birmingham B16 8ET.

Archives of Disease in Childhood, 1989, **64**, 413–418

Personal practice

The management of squint

A R FIELDER

Department of Ophthalmology, University of Leicester Medical School, Leicester

Squint may be the first sign of a serious ocular or systemic disorder, and yet it is also one of the most common ocular conditions of childhood. It follows that while most ocular deviations have no such sinister connotations, an understanding of the range of associations is essential to be prepared for this comparatively infrequent but important possibility.

Screening for squint has been covered recently[1] and in this article its presence will be assumed. The clinical evaluation of the child with a squint will be considered first, followed by a discussion of the aims and methods of treatment. The main thrust will be directed towards the squint itself, but as amblyopia is such a frequent and important association this topic will also be covered briefly. In order to avoid extensive and tedious repetition the associations of squint will be listed using a predominantly system based approach. Subdivision into paralytic and non-paralytic types is only done at a later stage as both may occur in certain categories. Inevitably this classification has limitations and inaccuracies, but hopefully it will help the paediatrician to consider the possible implications of a squint. For further reference the reader may wish to consult two excellent standard texts.[2 3]

In this article the following terms will be used interchangeably: squint and strabismus, esotropia and convergent squint, exotropia and divergent squint, comitant and non-paralytic squint, and incominant and paralytic squint. Comitance will be assumed unless the terms incominant or paralytic are used.

Squint and its associations

SQUINT AS AN ISOLATED ANOMALY

Recently emphasis has been placed on early referral of infants and children with squint, but this has not taken into account that during the neonatal period such a deviation may be a normal event. During early neonatal life about 32% of infants are divergent and only 3% convergent.[4] As the incidence of divergence is higher in preterm neonates it is likely that during development the eyes are initially divergent but that this resolves over the first few weeks of life.

Apart from those seen in the neonatal period, squints are comparatively uncommon in the first few months of life, and the term 'infantile' is preferred to 'congenital' because this type of esotropia is rarely if ever congenital but develops between 3 and 6 months of age. Characteristically the deviation is large, constant, and there is no appreciable refractive error.[5]

Apart from the infantile type, the onset of esotropia in childhood is most common between 1½ and 3 years of age. The deviation may range from the hardly detectable (microtropia) to the cosmetically obvious manifest squint, and may be intermittent or constant. In some the deviation increases—or is only present—on accommodation (partially and fully accommodative squints respectively). Many, but by no means all, are associated with refractive errors.

Exotropia is less common than esotropia at all ages and has less propensity to cause amblyopia. In infancy ocular divergence should alert the clinician to the possibility of a severe visual impairment.

Paralytic squints do occur as an isolated anomaly in an otherwise healthy child, but a careful search for an underlying cause must always be undertaken (see acute central nervous system disease). Most, but not all, paralytic squints in children are congenital rather than acquired, although the role of birth trauma as a causal factor has probably been greatly overemphasised. A sixth cranial nerve palsy may present at birth but characteristically this resolves over the ensuing few weeks. Apart from this clinically obvious and rare exception, the most common palsy, of the fourth nerve, is usually not diagnosed for a year or so as the ocular deviation is difficult to elicit in infancy and the presenting sign is usually a compensatory head posture. Third nerve palsy is less common but more obvious, and in children is more likely to be congenital than acquired. A form of the latter that usually commences in childhood is ophthalmoplegic migraine. Benign recurrent sixth nerve palsy, thought to be a post-infective mononeuropathy as it usually follows a febrile illness, is included here because at presentation there are no associated systemic or neurological signs.[6] In the superior oblique tendon sheath syndrome (Brown's syndrome) elevation of the eye in adduction is limited. The aetiology of this condition may differ between cases from a congenital anomaly of the tendon sheath to an acquired swelling of the tendon.

SQUINT AND OCULAR DISEASE

Squint may be the presenting sign of serious ocular disease. The eyes of a blind infant are commonly, but not invariably, divergent. Most important, squint either convergent or divergent may be the first sign of a treatable and potentially life threatening condition such as retinoblastoma. Thus squint can be associated with unilateral or bilateral ocular disease, including cataract and retinal disorders such as regressed retinopathy of prematurity (see below). Esotropia also develops in some children with congenital nystagmus.

SQUINT AND SYSTEMIC CONDITIONS

Many systemic conditions can be associated with strabismus and it would not be sensible or indeed possible to list them all here. Instead only a few will be considered and these will be grouped into broad categories.

Prematurity

The incidence of comitant squint is increased in infants born prematurely with figures quoted from 11% to 19%.[7–9] The pathogenesis of this association is not well understood but is almost certainly due in part to both the perinatal neurological insults and retinopathy of prematurity to which these infants are susceptible.[8] A high incidence of squint has also been reported in term and preterm infants who have had phototherapy for the treatment of hyperbilirubinaemia,[10] but a causal relationship between these two and squint has not been defined particularly as many of these babies will also have suffered the aforementioned complications.

Disorders of the central nervous system

Acute diseases of the central nervous system—The association between squint and acute serious disease of the central nervous system is well known, and it must always be remembered that it may be the first sign of serious neurological disease. The deviation may be unilateral, bilateral, and concomitant or paralytic, or both. Causes include raised intracranial pressure, intracranial tumours, trauma, degenerative and inflammatory diseases.[6 12]

Neurodevelopmental disorders—In general, the incidence of ocular abnormalities in children with neurodevelopmental disorders including Down's syndrome and cerebral palsy ranges from about 40% to 90%.[12] Of these squint is the most common with an average incidence of about 40%,[12–15] depending both on patient selection and the nature of the neurodevelopmental disorder. Although both comitant and incomitant deviations occur the former are far more common.

Brain stem dysfunction—Two conditions need to be considered in this category: Duane's and Möbius' syndromes. Duane's syndrome is relatively common and superficially resembles a sixth nerve palsy and its identification can obviate the need for extensive investigation Often an isolated anomaly, it can be associated with other congenital abnormalities such as Goldenhar's syndrome, spina bifida, and deafness. Möbius' syndrome is either a developmental defect or an acquired hypoxic insult to the cranial nerve nuclei and is characterised by bilateral facial weakness, horizontal gaze palsies, and esotropia in some cases. Affected children are usually mentally retarded, deaf, and exhibit limb malformations.

Muscle disease

Uncommon in routine clinical practice and can easily therefore be misdiagnosed. Extraocular muscle involvement in myasthenia usually involves the levator muscle of the eyelid resulting in ptosis and may also affect any other extraocular muscle leading to diplopia. Characteristically myasthenic symptoms increase with fatigue and the signs can be unilateral or bilateral. Ocular motility may be affected in other muscle disorders and esotropia may occur in myotonia congenita. Ophthalmoplegia is seen in a number of muscle disorders including congenital and other myopathies, dystrophia myotonia and mitochondrial cytopathy. As in these last mentioned conditions the limitation of ocular movements is usually symmetrical, diplopia is not a common symptom. Rarely only the extraocular muscles are involved as in the congenital fibrosis syndrome.

ORBITAL CONDITIONS

In this group of conditions certain ocular movements are limited, due not to a neurogenic cause, but to mechanical restriction of the muscle movement. Examples include injury such as orbital blow out fractures and infections. Squint may be the first sign of an orbital tumour such as rhabdomyosarcoma.

Investigation

Even now the evaluation of a squint, and its effect on the visual system, remains essentially clinical. The obvious priority is to identify first those conditions that require urgent treatment, and investigation should consequently be directed initially towards three aspects. First the type of squint, whether it is paralytic or non-paralytic, and either congenital or acquired; second, the identification of amblyopia; and third, the presence of associated pathology in the eye, orbit, or elsewhere. The extent of this spectrum has already been indicated and clearly the prevailing clinical conditions in an individual patient will dictate the relevance of each of these topics.

DETERMINING THE TYPE OF SQUINT

Differentiating the paralytic and non-paralytic squint is important and sometimes difficult. Exemplified by sudden onset squint a relatively common clinical dilemma in which determining the type (or even types) of squint is often difficult and can be at times impossible, particularly in the young fractious child.[16] A sudden onset is suggestive, but not pathognomonic, of paralysis and can also occur with non-paralytic deviations, and on occasion both types may coexist.

It is pertinent to review the natural history of paralytic strabismus, which at its onset is characterised by a deviation greatest in the direction of action of the paretic muscle. Over the ensuing weeks and months there is tendency for 'spread of comitance' to occur, with the deviation spreading to all positions of gaze, so that eventually it becomes indistinguishable from a comitant squint and the paretic muscle cannot be identified. The following points may help in distinguishing a recent from an old paresis, or comitant squint. Diplopia is a feature of a recent paresis but not of other types. Amblyopia is present in longstanding but not recent deviations and past pointing is a feature only of the latter. A compensatory head posture is often present in both new and old pareses, but rarely in a primary comitant squint, and the former two can readily be differentiated by scrutinising old photographs.

HISTORY

Ocular history

Diplopia indicates a recent onset deviation, usually paretic. If spontaneously volunteered by the patient it can usually be relied upon, but this symptom extracted by direct questioning must be treated with caution as children can confuse physiological and pathological diplopia. The term diplopia is also sometimes used to describe blurred vision, as in the uncorrected myope. As children relatively rarely complain of diplopia, indirect evidence such as closing one eye when looking in a particular direction can be helpful. Often there is a disparity between history and findings concerning the following signs: squint, ptosis, compensatory head posture, proptosis, and pupil inequality. In this situation a selection of photographs can be invaluable in distinguishing old from fresh pathology and obviate the need for extensive investigations.

General history

Information on pregnancy, perinatal history, and general development are obviously important, but for the readers of this article need not be stressed. Nevertheless as squint may be the first sign of a serious neurological or ocular abnormality, the history must take these possibilities into account.

EXAMINATION

Ophthalmic examination

Measurement of visual acuity is the first step, but this remains the Achilles heel of paediatric ophthalmology. Even at the age of 3½ years accurate measurement is often not possible using standard tests.[17] Preferential looking based techniques are opening important new horizons in clinical vision assessment, but as yet caution must be expressed regarding their accuracy in amblyopia measurement in the very young.[18] Therefore in this population, evaluation remains qualitative, relying on such observations as objection to the occlusion of one eye.

Look for any facial, orbital, eyelid, or ocular asymmetry. Surprisingly when this is present determining which side is abnormal may not be simple. Thus a mother's comment that the right eye is smaller could denote just that. It could also indicate the presence of a right ptosis, right enophthalmos, or left proptosis, all of which could, by different mechanisms, be associated with strabismus.

Assessment of the squint and ocular motility, including the cover test, is mandatory. Ocular movements must be tested in all positions of gaze, and while many paretic squints are obvious, during the recovery phase limitation of movement may be almost undetectable. In this instance further tests (for example, Hess chart) of overaction of the synergistic muscle of the other eye can be invaluable.

No ophthalmic examination is complete without assessment of the pupillary reactions, visual fields (when indicated) and fundoscopy. As many squints are associated with an abnormal refractive status, except where urgent clinical problems preclude, mydriatic refraction is an essential part of the assessment.

Systemic examination

Most squints occur as an isolated anomaly; however, the possibility of coexistent or causal systemic pathology must not be forgotten, and a detailed paediatric assessment undertaken if indicated.

ADDITIONAL INVESTIGATIONS

Having already indicated the range of conditions that can be associated with strabismus, the need for additional tests such as a Hess chart, tensilon test, muscle biopsy, or computed tomogram is dictated by the prevailing clinical conditions and will not be considered here.

Treatment

The aim of treatment is to restore binocular single vision. This single aim encompasses: rectifying and refractive error, the treatment of amblyopia, and finally correction of the ocular deviation. As in almost all young children with strabismus there is a risk of amblyopia, treatment is directed initially towards prevention or correction of this aspect, and then to the management of the deviation. Although complete restoration of normal visual functions is often not possible, significant and worthwhile improvement can usually be achieved.

TREATMENT OF AMBLYOPIA

Not all types of amblyopia behave similarly and here only general guidelines are included. The principle of all modalities of amblyopia treatment is to promote the use of the amblyopic eye by compromising the vision of the better eye. This is usually achieved by occlusion, but other commonly used methods include penalisation and the CAM stimulator. Treatment should commence at as early an age as possible, but a prerequisite to all amblyopia treatment is a clear retinal image, and consequently accurate optical correction is essential using either spectacles or contact lenses.

Occlusion of the better eye, by an adhesive occluder, is the most commonly used method of amblyopia treatment and this can be worn full time or part time. Full time occlusion requires careful monitoring as there is a danger of transient amblyopia developing in the initially non-amblyopic eye. Part time occlusion is generally preferred for durations of 30 minutes to three hours or more. One study that compared conventional (more than three hours a day) and minimal (30 minutes) occlusion, and the CAM stimulator (see below) found all three methods equally effective, although there was no improvement in 23%.[19] If no improvement was achieved with one method it was worth trying one of the alternatives.[19] If the amblyopia is refractory to treatment, as a last resort a short period of intensive occlusion on an inpatient basis may be undertaken. Occlusion is continued until either the visual acuity is restored to normal, or failing this, remains stable for at least three months. After cessation of treatment vision may deteriorate again in about 50% of cases,[20] and further periods of occlusion may be required. If amblyopia is to recur this usually occurs soon after the completion of treatment, but can be much later at about 12 to 13 years of age. Compliance is a common problem not surprising as occlusion is unpleasant particularly when the amblyopia is dense. Reported success rates vary: 77%,[19] 92%,[21] or 100%.[20] Flynn and Cassady reported success in only 56%, but their series included patients with form deprivation amblyopia, a particularly difficult group to treat.[22] Despite these varying success rates occlusion remains the mainstay and most effective form of treatment.

Two other types of amblyopia treatment in current use are penalisation and the CAM visual stimulator. In penalisation the vision of the better eye is blurred with either atropine or glasses, or a combination of these two. It can be used in amblyopia in the following situations: as the first line of treatment (not common), as an alternative when occlusion has failed, for maintenance of vision after successful occlusion, for recurrent amblyopia, and for children who refuse to wear an occlusive patch for cosmetic reasons.[2 3] The CAM visual stimulator consists of a rotating high contrast grating with a transparent cover over which the child draws. Each treatment session lasts only a few minutes. Although improvement does occur this cannot be attributed to the gratings per se, but to other factors, such as minimal occlusion of the better eye during treatment.[23]

TREATMENT OF SQUINT

As already mentioned the aim of squint treatment is the restoration of binocular function. Unfortunately, particularly in comitant deviations, this is often not possible, and the cynic could easily regard treatment as entirely cosmetic. Of course cosmesis is an important goal in itself but in some paralytic deviations normal binocular function can be restored, while in other types of squint useful but subnormal binocular function can be achieved. In this section the deviation will be assumed to be comitant unless otherwise specified, and because of the large range of conditions within this range treatment will only be discussed in broad terms.

Despite the knowledge that most squints are without any serious systemic or ocular overtones, this possibility must not be forgotten, and before correction of the ocular deviation is considered, the child should be adequately investigated.

Nonsurgical treatment

Optical—Refractive errors and squint are commonly associated, and for this reason every strabismic child should have a meticulous mydriatic refraction. Spectacles are prescribed for two distinct reasons: first to correct a visually important refractive error and to provide a clear retinal image—essential before embarking on amblyopia treatment. Second, to ensure reasonable balance between accommodation and convergence. In this latter situation spectacles are prescribed to rectify the ocular misalignment and not to correct a visual deficit. Certain deviations, such as fully accommodative esotropia, can be adequately controlled by spectacles, while for others the result is less satisfactory and surgery may then be indicated. The effect of refractive correction depends on the age of the patient and squint type, but even so is often difficult to predict and it is common practice to correct any 'significant' refractive error as an initial step before embarking on surgery. Prisms are rarely used in paediatric practice except perhaps temporarily to control diplopia in a paralytic squint.

Surgical treatment

Surgery to align the eyes is considered for the following reasons: to cure diplopia, correct a compensatory head posture, or most commonly to correct a squint either not associated with a refractive error, or when spectacles have not had the desired effect. General comments only will be made.

Paralytic squint—Whether the palsy is congenital or acquired, treatment is essentially surgical (having first corrected any amblyopia) aiming to correct either a compensatory head posture or diplopia. For an acquired palsy at least six months of recorded stability is mandatory before surgery is contemplated.

Comitant squint—Any significant refractive error is corrected first, even in the presence of normal visual acuities. The adage, amblyopia correction before surgical intervention, generally holds true and every parent must understand that surgical alignment will not improve visual acuity. Surgery for infantile esotropia is generally undertaken between 6 months and 2 years of age as correction after this time achieves less in terms of binocular function. Surgery for cosmetic reasons can be performed at any age although the needs of an individual child will dictate the timing of this.

A group which requires particular attention is that with neurodevelopmental problems. As with all cases of strabismus the appropriate refractive correction should be considered first otherwise the result after surgical intervention can be disappointing.[24] If surgery is undertaken the amount of extraocular muscle surgery necessary to achieve the same result needs to be less in the retarded compared with the normal child. In the past there has been a general reluctance to consider cosmetic surgery for these children, but the results can be rewarding for the child, parent, and others in daily contact.[12] Under these circumstances it is not the role of the surgeon to advise surgery, but simply ensure that parents understand the various therapeutic options, their benefits and limitations.

Treatment of special types of squint—The management of other types such as Duane's syndrome, superior oblique tendon sheath syndrome, and those due to muscle or orbital disease, cannot be considered in detail here. Some of these conditions produce no symptoms or little cosmetic defect (for example, most cases of Duane's syndrome) and clearly do not require treatment, while for others surgery may be considered to reduce or correct the strabismus or head posture, or increase the field of binocular single vision.

Botulinum toxin

This neurotoxin produces a temporary paralysis when injected into muscle and has been used as an alternative to extraocular muscle surgery over the past eight years. It is particularly effective in palsies, but has also been used in comitant deviations. To date its use in children is limited,[25 26] but in the future it may well find an important niche in the management of paediatric strabismus.

Conclusion

While in most children squint is an isolated abnormality, it can also be the consequence of, or associated with, a large variety of other conditions. Clinical evaluation is not always straightforward and it is imperative that when there is the possibility of additional pathology the appropriate multidisciplinary assessment is adopted. In general, treatment is directed first to the correction of amblyopia and secondarily to the deviation itself.

References

[1] Taylor D. Screening for squint and poor vision. *Arch Dis Child* 1987;**62**:982-3.

[2] Von Noorden GK. *Burian-Von Noorden's binocular vision and ocular motility*. 3rd ed. St Louis: CV Mosby, 1985.

[3] Mein J, Harcourt B. *Diagnosis and management of ocular motility disorders*. Oxford: Blackwell Scientific Publications, 1986.

[4] Nixon RB, Helveston EM, Miller K, Archer SM, Ellis FD. Incidence of strabismus in neonates. *Am J Ophthalmol* 1985; **100**:798–801.

[5] Von Noorden GK. A reassessment of infantile esotropia. XLIV Edward Jackson Lecture. *Am J Ophthalmol* 1988;**105**:1–10.

[6] Bixenman WW, von Noorden GK. Benign recurrent VI nerve palsy in childhood. *J Pediatric Ophthalmol Strabismus* 1981;**18**: 29–34.

[7] Kitchen WH, Ryan MM, Rickards A, *et al.* A longitudinal study of very low-birthweight infants IV. An overview of performance at eight years of age. *Dev Med Child Neurol* 1980;**22**:172–88.

[8] Kushner BJ. Strabismus and amblyopia associated with regressed retinopathy of prematurity. *Arch Ophthalmol* 1982;**100**: 256–61.

[9] Keith CG, Kitchen WH. Ocular morbidity in infants of very low birth weight. *Br J Ophthalmol* 1983;**67**:302–5.

[10] Moseley MJ, Fielder AR. Light toxicity and the neonatal eye. *Clinical Vision Sciences* 1988;**3**:75–82.

[11] Harcourt B. Guidelines in the management of incomitant strabismus in children. In: Wybar KC, Taylor D, eds. *Pediatric ophthalmology: current aspects*. New York: Marcel Dekker Inc, 1983:341–54.

[12] Hiles DA, Waller PH, McFarlane F. Current concepts in the management of strabismus in children with cerebral palsy. *Ann Ophthalmol* 1975;**7**:789–98.

[13] Harcourt B. Strabismus affecting children with multiple handicaps. *Br J Ophthalmol* 1974;**58**:272–80.

[14] Bankes JLK. Eye defects of mentally handicapped children. *Br Med J* 1974;**ii**:533–5.

[15] Milot J, Guimond J. Strabismus as an expression of cerebral motor dysfunction in childhood. *Clin Pediatr* 1977;**16**:477–9.

[16] Watson AP, Fielder AR. Sudden-onset squint. *Dev Med Child Neurol* 1987;**29**:207—11.

[17] Shaw DE, Fielder AR, Minshull C, Rosenthal AR. Amblyopia—factors influencing age at presentation. *Lancet* 1988;**ii**:207–9.

[18] Mayer DL, Fulton AB, Rodier D. Grading and recognition acuities of pediatric patients. *Ophthalmology* 1984;**91**:947–53.

[19] Watson PG, Sanac AS, Pickering MS. A comparison of various methods of treatment of amblyopia: a block study. *Trans Ophthalmol Soc UK* 1985;**104**:319–28.

[20] Ching FC, Parks MM, Friendly DS. Practical management of amblyopia. *J Pediatr Ophthalmol Strabismus* 1986;**23**:12–6.

[21] Scott WE, Dickey CF. Stability of visual acuity in amblyopic patients after visual maturity. *Graefes Arch Clin Exp Ophthalmol* 1988;**226**:154–7.

[22] Flynn JT, Cassady JC. Current trends in amblyopia therapy. *Ophthalmology* 1978;**85**:428–50.

[23] Keith CG, Howell ER, Mitchell DE, Smith S. Clinical trial of the use of rotating grating patterns in the treatment of amblyopia. *Br J Ophthalmol* 1980;**64**:597–606.

[24] Lo Cascio GP. Treatment for strabismus in cerebral palsy. *Am J Optom Physiol Opt* 1987;**64**:861–5.

[25] Magoon EH. Botulinum toxin chemo-denervation for strabismus in infants and children. *J Pediatr Ophthalmol Strabismus* 1984;**21**:110–3.

[26] Scott AB. Botulinum injection treatment of congenital esotropia. In: Lenk-Schafer M, ed. *Transactions of the sixth international orthoptic congress*. 1987:294–9.

Correspondence to Professor AR Fielder, Birmingham and Midland Eye Hospital, Church Street, Birmingham B3 2NS.

Archives of Disease in Childhood, 1989, **64,** 419–422

Contemporary history

Oral rehydration therapy: an epithelial transport success story

W B GREENOUGH III

Division of Geographic Medicine, Johns Hopkins University, Baltimore, USA

Oral rehydration therapy prevents death in acute watery diarrhoea except in the most severe 1–3% of cholera cases. If started at the onset of illness, weakness, orthostasis, muscle cramps, lethargy, and other symptoms of a contracted circulating blood volume are entirely prevented.[1] Poor countries have rapidly expanded their use of this practical and inexpensive treatment[2] while it has been largely neglected in wealthy nations in favour of the more hazardous and costly luxury of hospitalisation and intravenous therapy. Improved solutions are now emerging that not only rehydrate patients, but also reduce severity and shorten illness.[3] To grasp this opportunity basic physiological research on the intestinal transport of amino acids, dipeptides and tripeptides, and clinical studies of solutions which optimise all cotransport pathways and minimise lumenal osmotic forces are needed. Such research should be connected to practical field trials of improved oral rehydration solutions.

Of the origin of oral rehydration therapy it can be said that nothing is discovered unless it is already known. As it is a decisively effective treatment based on ingredients in common foods and drinks, glimpses of benefit have been repeatedly observed in many countries in what may be called 'grandmother solutions'. The earliest recorded reference I have found is from Vedic texts.[4] All such home solutions take partial and unwitting advantage of the potent cotransport capacity of the intestine which links the absorption of salt, water, and certain solutes. Unfortunately the empirical knowledge embodied in folk remedies before the scientific discovery of intestinal cotransport and its application to the correct formulation and administration of oral hydration solutions was rarely sufficient to prevent many deaths from diarrhoea. Few 'grandmother solutions' were constituted adequately to tread the path of effective hydration without the hazards of hypertonicity or hypotonicity. The commonest oversight in their use was failure to adequately replace losses. Few family members ever thought of drinking the several gallons of soup that may be essential to replace losses in severe cases of diarrhoea.

The scientific basis for oral rehydration therapy evolved in physiology and biophysics laboratories from the late 1940s to the early 1960s. Of particular note were early observations from Oxford University by Parsons and Fisher who first showed in an in vitro preparation of rat small intestine that glucose enhanced the absorption of water.[5] Later the biophysical laboratories of Harvard University fostered investigations of Curran[6] and Crane.[7] A full articulation of the obligatory transport of sodium ions with glucose molecule independent of any metabolism of glucose probably rests with Schultz and Zalusky in 1962 working at the United States Air Force School of Aerospace Medicine.[8] Had the funding agencies who provided the support needed to carry out esoteric in vitro research on basic transport processes been seeking a way to alleviate death and suffering of the world's children it is unlikely they would have chosen to support the very investigations that made oral rehydration therapy possible.

Concurrently with the basic science that was in progress in England and the United States there was a resurgent interest in the problems surrounding clinical cholera. Crucial early studies by United States Naval Medical Research Units led by Captain Robert Phillips, first in Egypt in 1947 then in Thailand in 1958, led to an accurate understanding of the pathophysiology of cholera.[9] This provided a firm foundation for understanding other diarrhoeal illnesses and stimulated the establishment by the United States National Institutes of Health of two research units in the midst of cholera endemic areas. One of these was The Pakistan-SEATO Cholera Research Laboratory (now The International Centre for Diarrhoeal Disease Research, Bangladesh) in Dhaka, Bangladesh. The other was the

Johns Hopkins University International Center for Medical Research and Training in Calcutta, India. Investigators at these units were aware of current research in physiology and biochemistry and rapidly advanced understanding of cholera and related it to other diarrhoeas.[10] Clinical research was linked to patient care and the situations in Dhaka and Calcutta made it obvious that although proper intravenous fluid therapy could guarantee survival of cholera patients, it was equally clear that the vast majority of patients with cholera and cholera like illnesses would never have access to intravenous technology nor be able to afford it.[11 12] Thus the large numbers of untreated and dying cholera patients provided an enormous stimulus to the search for successful oral hydration solutions.

Early attempts in the Phillipines by Dr Phillips and his colleagues met with some success in showing that glucose could produce net fluid absorption in patients with cholera, but they failed because of excessive sodium concentrations in the solutions, which produced hypernatraemia.[10] Careful intubation studies were then done in Dhaka to define electrical potential changes and ion fluxes produced by glucose-electrolyte solutions of varying composition perfused into actively purging cholera patients.[13] Subsequently both in Dhaka and Calcutta orogastric glucose-electrolyte solutions with well defined boundaries of composition were perfused into actively purging cholera patients and it was shown that oral solutions could successfully rehydrate and maintain hydration.[14 15] In late 1967 and 1968 treatment of patients, first in the hospital and later in a rural area of Bangladesh, was successful.[16 17] By 1971 application of oral rehydration therapy to large numbers of victims under the most adverse conditions during the exodus of refugees from war torn Bangladesh was highly successful. Death rates of untreated cholera among refugees were between 30 and 50%. With oral rehydration therapy administered by briefly trained volunteers and packaged in the library at the Johns Hopkins University International Center for Medical Research and Training in Calcutta death rates dropped to less than 3%. In an area where there was medical supervision and where intravenous fluid was used for early rehydration of the most severe cases, mortality was less than 1%.[18]

Investigators returning to the United States from Dhaka and Calcutta continued studies on cholera and oral rehydration therapy. In rapid succession the mechanism of action of cholera toxin was shown[19] and the toxin purified.[20] Other related toxins were discovered.[21] The cotransporting capacity of the intestinal epithelium was shown not to be affected by any of the mechanisms producing the vast majority of diarrhoeal illness in the world. A rapid consensus was developed under the aegis of the World Health Organisation (WHO) concerning the composition of a standard solution for oral rehydration therapy.[22] By 1978 the global importance of diarrhoeal diseases was recognised as WHO formed a Control Programme for Diarrhoeal Diseases[23] and the Cholera Research Laboratory in Dhaka was reconstituted as the International Centre for Diarrhoeal Diseases Research, Bangladesh.[10] A concerted effort has resulted in the majority of poor countries adopting national programmes for control of deaths due to diarrhoea and diarrhoeal diseases.

With these solid accomplishments have come a series of issues including:

(1) Continuing dialogue and investigations of the safe and effective compositional boundaries of solutions being used for oral rehydration therapy. Fortunately when used early and in sufficient volumes normal renal perfusion is maintained. The resultant sustained normal renal function permits considerable latitude.

(2) The formidable practical problems of storage with timely distribution to those in need coupled with assured safe preparation remain challenging.

(3) The place of home solutions of widely varying compositions and instructions for preparation still confounds most national programmes. Thus some excellent and available oral hydration solutions are relegated to obscurity.

(4) The best way to train those who will subsequently train others to propagate the most effective use of oral rehydration therapy presents many alternatives, all of which require evaluation.

(5) Solutions with improved performance that shorten diarrhoea and improve nutrition are emerging rapidly. Decisions on how and when to advocate these in place of the now standard WHO/United Nations Childrens Fund (Unicef) oral rehydration solution present a problem.

Now in 1989 there are enormous opportunities and with these formidable challenges. Perhaps the first challenge is an urgent need to return to the basics of transport dynamics—the original source of oral rehydration therapy. We have been aware that besides glucose there are other independent cotransport pathways that have not been adequately explored. Amino acids, dipeptides and tripetides, and other compounds all depend on the sodium ion for their absorption by the gut.[24] Early studies tested glycine,[25] and more recently alanine has been tested in solutions for oral replacement therapy.[26] It is clear that these and other amino acids will stimulate the transport of sodium additively to glucose at low concentrations. We need to know the theoretically optimal mix of glucose, peptides, amino acids, and any other compounds important to the transport functions and integrity of intestinal epithelium. We are lacking much of this information. Even with this knowledge, however, there is a very serious obstacle to overcome. The intestine has a very permeable or 'leaky' epithelium exquisitely sensitive to osmotic and hydrostatic forces.[27 28] Thus oral rehydration solutions must be designed to have the lowest possible osmotic activity to minimise osmotic restraints to the transit of water from the lumen into the blood and lymphatics.[29]

The digestive system as a whole provides an extraordinary opportunity to solve the osmotic constraint. It is designed to accept polymers and degrade them at a rate and locus that minimises the accumulation of cleaved small molecules in the gut lumen. In the common diarrhoeal illnesses digestive enzymes which cleave starches and proteins are present in excess perhaps due to the hypersecretory nature of the diseases and their mediators. Thus we can present salt and water to the intestine together with cotransport molecules linked as large osmotically inactive polymers. The problem and possibility then is to define which starches and which proteins provide the best and most digestible mixture of the ultimately desired cotransporting glucose and amino acids. Or more simply stated—what foods are available locally in any situation that will best provide the needed substances to promote solute absorption? Thus science returns to the 'grandmother solutions' but with a very clear agenda in mind.

Observations from the International Centre for Diarrhoeal Diseases Research in Dhaka in 1978 that solutions for oral rehydration therapy based on rice powder were at least as effective as glucose based solutions[30] have been widely confirmed. Many studies have now shown that both the severity and duration of diarrhoea are considerably reduced and vomiting controlled by cereal based solutions.[31 32] At present one field trial has been completed that appears to confirm the results of clinical trials—that there are significant advantages to cereal based solutions.[33]

As yet there are no studies that have looked at the kind or amount of proteins needed for optimal absorption of salt and water. It is not known how much the proteins present in the cereals contribute to the improved performance of cereal based oral rehydration solutions. This is a frontier in urgent need of exploration.

Finally it is important to emphasise that the main reason that the use of digestible polymers improves the performance of these solutions is that more cotransporting molecules can be made available with little or no osmotic penalty. Thus solutions such as rice water or other dilute starch or protein solutions for oral rehydration fail to make use of the main rationale for which a cereal based solution was introduced. Because of the fortunate finding that natural food polymers outperform commercially processed monomers there is a real risk of confusion and relapse to a potpourri of ineffective or inadequate home solutions. The principle of providing maximum cotransporting molecules at the lowest lumenal osmolality with the correct concentrations of salts and giving enough to replace all losses must be kept clearly in focus, taught effectively, and propagated without distortion for the fullest and most effective application of oral rehydration therapy.

The future holds several promises if we do our job properly. First and foremost, except under true famine conditions, all households now have cereals and salt with which effective oral rehydration solutions can be made. Communication of knowledge is needed and when successful there will be few deaths due to acute watery diarrhoea. Second it is likely that through research and the technology of the food processing industries a new family of polymeric solutions can be produced and conveniently packaged at low cost. Third it is likely that even wealthy 'developed' countries may adopt early use of oral rehydration therapy in diarrhoea and there will be great savings in the unnecessary hospitalisations now required for intravenous replacement therapy. This will reduce complications that accompany hospitalisation and indwelling vascular lines.

There will of course be many problems and controversies about how best to make use of what we know. I have entirely avoided crucial issues in the treatment of diarrhoea—that is, nutrition and what and when to feed. Implicit in what I have said about food polymers and oral rehydration therapy, however, is the fact that feeding should accelerate the resolution of diarrhoeal illnesses. This is largely true and many would say that there is no need of food based oral rehydration—we can simply use standard glucose based solutions and feed proteins and complex carbohydrates. This is in fact a viable alternative that is being explored.[34] If food polymers are used for oral rehydration solutions when does one feed? My current answer is as soon as a patient is able and willing to eat. What to feed is a large area of concern and inquiry of itself.[35]

The special problems of treating neonates or premature babies have not been addressed in this discussion. How successfully oral rehydration therapy can be pressed for the treatment of the youngest infants still demands further work. That breast feeding can and should be maintained is very clear. It should be noted, however, that there may be an added margin of safety in the polymer based oral rehydration solutions. If not cleaved by digestive action the starches and proteins pass rapidly out without the hazard of osmotic diarrhoea because of their intrinsically low osmolality.

This paper was presented at the Annual Meeting of the British Paediatric Association in York, 12–15 April 1988.

References

[1] Cash RA, Nalin DR, Forrest JN, Abrutyn E. Rapid correction of acidosis and dehydration of cholera with an oral electrolytes and glucose solution. *Lancet* 1970;**ii:**549–50.

[2] Grant JP. *The state of the world's children 1988.* Oxford: Oxford University Press, 1988: 19–22. (Published for Unicef.)

[3] Carpenter CCJ, Greenough WB III, Pierce NF. Oral rehydration therapy: Role of Polymeric Substrates. *N Engl J Med* 1988; **319:**1346–8.

[4] *Sushruta Samhita.* Vol III. *Chowkamba Sanskrit Studies.* Vol XXX. English translation by Kaviraj Kinjalai Bhishgrantha Chowkamba. 3rd ed. Varanasi, India: Sanskrit Sources Office, 1981.

[5] Fisher RB, Parsons DS. Glucose movements across the wall of the rat small intestine. *J Physiol* 1953;**119:**210–23.

[6] Curran PF. Na, Cl, and water transport by rat ileum in vitro. *J Gen Physiol* 1960;**43:**1137–48.

[7] Crane RK. Na+-dependent transport in the intestine and other animal tissues. *Fed Proc* 1965;**24:**1000–6.

[8] Schultz SG, Zalusky R. Ion transport in isolated rabbit ileum II: the interaction between active sodium and active sugar transport. *J Gen Physiol* 1964;**47:**1043–59.

[9] Phillips RA. Water and electrolyte losses in cholera. *Fed Proc* 1964;**23:**705–12.

[10] Van Heyningen WE, Seal JR. *Cholera: the American scientific experience, 1947–1980.* Boulder, Colorado: Westview Press, 1983.

[11] Gordon RS Jr, Feeley JC, Greenough WB III, Sprinz H, Oseasohn R. Cholera. *Ann Intern Med* 1966;**64:**1328–51.

[12] Carpenter CCJ, Mondal A, Sack RB, *et al.* Clinical studies in Asiatic cholera II: development of 2:1 saline:lactate regimen. Comparison of this method with traditional methods of treatment April-May 1963. *Bulletin of Johns Hopkins Hospital* 1966;**118:**174–96.

[13] Sachar DB, Taylor JO, Saha JR, Phillips RA. Intestinal transmural electric potential and its response to glucose in acute and convalescent cholera. *Gastroenterology* 1969;**56:**512–31.

[14] Hirschhorn N, Kinzie JL, Sachar DB, *et al.* Decrease in net stool output in cholera during intestinal perfusion with glucose-containing solutions. *N Engl J Med* 1968;**279:**176–81.

[15] Pierce NF, Banwell JG, Mitra RC, *et al.* Effect of glucose-electrolyte infusion upon water and electrolyte balance in Asiatic cholera. *Gastroenterology* 1968;**55:**333–43.

[16] Cash RA, Nalin DR, Rochat R, Reller LB, Haque Z, Rahman ASMM. A clinical trial of oral therapy in a rural cholera treatment center. *Am J Trop Med Hyg* 1970;**19:**653–6.

[17] Pierce NF, Sack RB, Mitra RC, *et al.* Replacement of water and electrolyte losses in cholera by an oral glucose electrolyte solution. *Ann Intern Med* 1969;**70:**1173–81.

[18] Mahalanabis D, Choudhuri AB, Bagchi NG, Battacharya AK, Simpson TW. Oral fluid therapy of cholera among Bangladesh refugees. *Johns Hopkins Medical Journal* 1971;**132:**197–205.

[19] Field M. Intestinal secretion: effect of cyclic AMP and its role in cholera. *N Engl J Med* 1971;**284:**1137–44.

[20] Finkelstein RA, Lospalluto JJ. Production of highly purified choleragen and choleragenoid. *J Infect Dis* 1970;**121**(suppl): S63–72.

[21] Gyles CL. Relationships among heat labile enterotoxins of Escherichia coli and Vibrio cholerae. *J Infect Dis* 1974;**129:**277–83.

[22] Pierce NF, Hirschhorn N. Oral fluid—a simple weapon against dehydration: how it works and how to use it. *WHO Chron* 1977;**31:**87–93.

[23] Snyder JD, Merson MH. The magnitude of the global problem of acute diarrhoeal disease: a review of active surveillance data. *Bull WHO* 1982;**60:**605–13.

[24] Field M. New strategies for treating watery diarrhoea. *N Engl J Med* 1977;**297:**1121–2.

[25] Nalin DR, Cash RA, Rahman M, Yunus M. Effect of glycine and glucose on sodium and water absorption in patients with cholera. *Gut* 1970;**11:**768–72.

[26] Wapnir RA, Zdanowicz MM, Teichberg S, Lifshitz F. Oral hydration solutions in experimental osmotic diarrhea: enhancement by alanine and other amino acids and oligopeptides. *Am J Clin Nutr* 1988;**48:**84–90.

[27] Fordtran JS, Locklear TW. Ionic constituents and osmolality of gastric and small intestinal fluids after eating. *American Journal of Digestive Disease* 1966;**11:**503–21.

[28] Wapnir RA, Lifshitz F. Osmolality and solute concentration—their relationship with oral hydration solution effectiveness: an experimental assessment. *Pediatr Res* 1985;**19:**894–8.

[29] Greenough WB III. Status of cereal-based oral rehydration therapy. *J Diarrhoeal Dis Res* 1987;**5:**275–8.

[30] Molla AM, Sarker SA, Hossain M, Molla A, Greenough WB III. Rice-powder electrolyte solution as oral therapy in diarrhoea due to Vibrio cholerae and Escherichia coli. *Lancet* 1982;**i:**1317–9.

[31] Molla AM, Ahmed SM, Greenough WB III. Rise-based oral rehydration solution decreases the stool volume in acute diarrhoea. *Bull WHO* 1985;**63:**751–6.

[32] Patra FC, Mahalanabis D, Jalan KN, Banerjee P. Is oral rice electrolyte solution superior to glucose electrolyte solution in infantile diarrhoea? *Arch Dis Child* 1982;**57:**910–2.

[33] Ahmed HS, Molla AM. Rice-based oral rehydration. *J Diarrhoeal Dis Res* 1987;**5:**1–6.

[34] Santosham M, Foster S, Reed R, *et al.* Role of soy-based, lactose-free formula during treatment of acute diarrhea. *Pediatrics* 1985;**76:**292–8.

[35] Brown KB, Maclean WC. Nutritional management of acute diarrhea: an appraisal of the alternatives. *Pediatrics* 1984;**73:**119–25.

Correspondence and reprint requests to Professor WB Greenough III, Division of Geriatric Medicine, Francis Scott Key Medical Center, 5200 Eastern Avenue, Baltimore, MD 21224, USA.

Archives of Disease in Childhood, 1989, **64,** 423

Neonatology—then and now (*CHM Walker*)

C reactive protein (1957)

The significance of the C reactive protein estimation in streptococcal and allied disease

SHEILA F DAWSON

Booth Hall Children's Hospital, Manchester (*Arch Dis Child* 1957;**32:**454–60)

By the time this paper was published the existence of C reactive protein had been known for at least 27 years—that is, almost 60 years ago. While originally thought to be a specific antibody against the pneumococcus it was eventually found in humans as a serum reaction to numerous inflammatory conditions and to tissue necrosis. This paper described the further purification by crystallisation of the protein and the production on a commercial scale of a specific antiserum for C reactive protein.

The claim is made that 'the use of this antiserum makes the detection of C reactive protein in serum a simple test' and describes its value in streptococcal and related disorders. Despite the claims that the new test was both qualitative and quantitative (reading a column of precipitate) the fact that the introduction states that C reactive protein 'is absent from normal serum' indicates that it could not have been a very sensitive test at that time. **Today.** It is now known that C reactive protein is only one of several plasma proteins of hepatic origin that increase in concentration in response to tissue inflammation, and the current interest in the newborn is its value in the detection of infection. White blood cell counts and ratios and erythrocyte sedimentation rates (with some recent reservations[1]) have on the whole proved adequate in older patients to establish the presence of active inflammation and C reactive protein has been used more to detect other forms of tissue damage, for example, in rheumatic disease. In the newborn, however, white blood cell counts and erythrocyte sedimentation rates are 'fickle friends' because of the wide physiological and pathological variations in red and white cell counts and plasma protein concentrations. Thus serial C reactive protein estimations, even measured semiquantitatively, have come into use with some success in aiding the detection of infection.

Though C reactive protein is the most easily measured reactant it has until recently been a poorly standardised semiquantitative test but its overall value should improve now that an international reference standard is available. Several rapid quantitative assays are now used and it has a singular advantage of responding vigorously within 6–10 hours of the onset of bacterial (though not viral) infection.[2]

Of the other acute phase reactants that have been studied in rheumatic diseases the mucoprotein tyrosine has been shown to be more 'stable' in the face of treatments with antibiotics and steroids. If micro methods were available for some of these other reactants they might assist even more than C reactive protein or plasma viscosity in establishing the presence of active infection in the newborn—or is it easier just to treat all preterm babies prophylactically with wide spectrum antibiotics? Even if the latter course is adopted such tests might help to identify those babies who were 'escaping' from such protection and to recognise the need for a change in antibiotic. Nitroblue tetrazolium and an acridine orange leucocyte cytosine test are also being studied in the apparently never ending search for a reliable, preferably single, test for neonatal infection.[3]

References

[1] Stuart J, Lewis SM. Monitoring the acute phase response. *Br Med J* 1988;**297:**1143–4.

[2] Stuart J, Whicher JT. Tests for detecting and monitoring the acute phase response. *Arch Dis Child* 1988;**63:**115–7.

[3] Kite P, Millar MR, Gorham P, Congdon P. Comparison of five tests used in diagnosis of neonatal bacteraemia. *Arch Dis Child* 1988;**63:**639–43.

Sheila Dawson is a graduate of the University of Leeds (1949) who despite family obligations continued her interest in paediatrics. At the time of writing this article she was part time clinical research assistant to the late Professor Aron Holzel at Booth Hall Children's Hospital, Manchester, the paper appearing in the *Archives* in the same month in which her second child was born. After a period out of medicine she returned as part time clinical assistant in haematology with a concomitant part time appointment in paediatrics, latterly moving to the paediatric section of community medicine. Her son, Dr David Oleesky, has continued her interest in immunology and has written on the subject of complement C 9.

Archives of Disease in Childhood, 1989, **64,** 424–430

Correspondence

The future of the BPA

Sir,

I have read Dr Forfar's personal paper with sadness and surprise. His view of the story of paediatrics and the Royal Colleges of Physicians, at least as far as this College is concerned, is based on misunderstanding and misinformation. The statements that the Joint Paediatric Committee was 'not allowed to develop', and that ultimate authority is 'vested in committees controlled by physicians concerned with adults' are simply erroneous. Authority in this College lies with Comitia to which all Fellows have full access. Also untrue is the statement that unlike the democratic BPA, the College and Comitia of this College have not had full opportunity to discuss the situation. Dr Forfar was on the Council of this College and if he thought our discussions on these issues were inadequate he could easily have enlarged them.

Let me summarise the position of this College with regard to the future of paediatrics. We support the aims of the BPA and are as concerned as they are with the future of paediatrics. We believe that it should lie within the general body of medicine, not in a separate College which we think would divide and weaken paediatrics and general medicine. We explained this to Dr Forfar, then President, and Dr T L Chambers, the Secretary of the BPA, when they came to see College Officers a couple of years ago. We said that the College would, however, welcome a suggestion of a Joint Faculty and do all we could to help it forward. Dr Forfar seemed at the time to welcome these views. We did not take any initiative thereafter as clearly that lay with the paediatricians—if we had done so we might well have been accused of interfering in the affairs of the BPA. Indeed, the College has had no proposal from the BPA until recently, after Dr Forfar wrote his article, when the present President of the BPA wrote to the President.

The position of paediatrics in this College at present is that there is always a paediatric censor, one of the three representatives on the Joint Consultants' Committee is a paediatrician and, in response to a BPA initiative, we have now created paediatric Regional Advisers who had their first meeting in October.

We were under the impression that we had met all the paediatricians' requests and are at a loss to understand Dr Forfar's evident sense of grievance.

We are anxious to find a way forward that will be in the interest of children and their doctors, and which will keep paediatrics and general medicine as closely together as possible.

D A Pyke
Registrar,
Royal College of Physicians,
11 St Andrew's Place,
London NW1 4LE

Inner city tuberculosis and immunisation policy

Sir,

I read with interest the article by Cundall and Pearson on neonatal BCG immunisation.[1] Although I applaud their conclusion that poverty may be a better indicator than ethnic origin of the risk of contracting tuberculosis I fear that this conclusion is based on a misleading analysis of their data. They tell us that it is policy (with an 86% uptake) in Leeds to immunise Asian children with BCG. Therefore they are comparing immunised Asian children with unprotected white children. If one calculates a rate for Asian children who are not vaccinated (910 children) it comes to an annual rate of 44 cases per 100 000 compared with their rate for white children of 5·5 (assuming that BCG is 100% effective). Taking their lower quoted figure for protection of 64% this leaves a total unprotected Asian population of 2922 and therefore an annual rate of 13·7 cases per 100 000. This is still 2·5 times greater than the rate for white children. A similar calculation (assuming 64% protection) results in a rate of 10·7 (their rate 10·0) for the urban priority area and 3·9 (their rate 3·9) for the non-urban priority area.

I would suggest that this analysis of their figures, which although crude does attempt to compare unprotected Asian and white children, supports the conclusion that immunising Asian children at birth reduces the incidence of tuberculosis in that group but does not support their conclusion that poverty is a better indicator than ethnic group of the risk of tuberculosis in childhood (Asian rate 13·7, urban priority area rate 10·7). These figures still support the idea that an expansion of neonatal BCG immunisation to include all children from the more disadvantaged areas is worthy of consideration. However, to show that ethnic groups are less at risk than people from poorer areas we would need a proper comparison of similar groups which this study clearly is not.

Reference

[1] Cundall D, Pearson S. Inner city tuberculosis and immunisation policy. *Arch Dis Child* 1988;63:964–5.

D Vickers
Royal Victoria Infirmary,
Queen Victoria Road,
Newcastle upon Tyne NE1 4LP

Drs Cundall and Pearson comment:

We thank Dr Vickers for his interest in our study. We do not think that our analysis of the data was misleading. We have stated clearly that our policy of BCG immunisation of Asian infants was one of the factors which contributed to the relatively small number of Asian children with active tuberculosis. The further analysis of our data by Dr Vickers is valid, but does not detract from our conclusion that tuberculosis was more common in poor children than in Asian children.

Ribavirin in respiratory syncytial virus infection

Sir,

Over the winter of 1988, 10 infants with congenital heart disease were treated for severe bronchiolitis at Guy's Hospital. All required respiratory support of greater than 50% oxygen in a headbox, and seven required assisted ventilation. Seven patients were positive for respiratory syncytial virus, and seven received nebulised ribavirin for three to five days. There were four deaths, all infants with pre-existing pulmonary hypertension (see table).

Despite the early use of nebulised ribavirin, supervised by Brittania Pharmaceuticals Ltd, some patients continued to deteriorate. Only three patients showed some improvement after ribavirin use. No patient improved when ribavirin was first used after ventilation had commenced. Indeed one child had an unexplained cardiorespiratory collapse on the ventilator shortly after starting ribavirin. We documented no other possible side effects.

We wish to emphasise the severity in Britain of respiratory syncytial virus bronchiolitis in infants with congenital heart disease. The high mortality in the presence of pulmonary hypertension confirms earlier American reports.[1] Our clinical impression was that ribavirin, started very early in the disease 'may' prevent some infants progressing to respiratory failure. The outcome was never one of dramatic clinical improvement.

The resource implications of widespread early use of ribavirin in all mildly symptomatic infants are very great however (approximately £600 for a three day course). We therefore strongly support the call for randomised controlled trials of ribavirin in bronchiolitic infants with cardiopulmonary disease.[2]

Table *Clinical details of 10 infants studied*

Case No	*Congenital heart disease*	*Respiratory syncytial virus*	*Assisted ventilation given*	*Ribavirin given*	*Outcome*
1	Total anomalous pulmonary venous drainage	+	Yes	Yes	Died
2	Patent ductus arteriosus	+	Yes	Yes	Alive
3	Double outlet right ventricle	+	Yes	Yes	Died
4	Total anomalous pulmonary venous drainage	+	No	Yes	Alive
5	Aortic stenosis, mitral incompetence	+	No	Yes	Alive
6	Ventricular septal defect	+	No	Yes	Alive
7	Pulmonary stenosis	+	Yes	No	Alive
8	Atrioventricular septal defect		Yes	Yes	Died
9	Ventricular septal defect		Yes	No	Alive
10	Ventricular septal defect		Yes	No	Died

References

[1] MacDonald NE, Hall CB, Suffin SC, Alexson C, Harris PJ, Manning JA. Respiratory syncitial virus infection in infants with congenital heart disease. *N Engl J Med* 1982;**307**:397–400.

[2] Isaacs D, Moxon ER, Harvey D, *et al.* Ribavirin in respiratory syncitial virus infection. A double blind placebo controlled trial is needed. *Arch Dis Child* 1988;**63**:986–7.

M SHARLAND, N WHITEHOUSE, *and* S QURESHI
Guy's Hospital,
St Thomas Street,
London SE1 9RT

Lung function and bronchial responsiveness measured by forced oscillometry after bronchopulmonary dysplasia

Sir,

We were interested to read the recent report by Duiverman *et al* on lung function in the long term survivors of bronchopulmonary dysplasia.[1] Their results differ from those of previous small studies and one large series[2] in that they failed to find an increase in airway responsiveness to inhaled histamine. Although differences in protocols and techniques used in these studies make direct comparison difficult, we feel that the main problem was technical rather than physiological.

The incidence of a positive airway response to pharmacological challenge depends on the arbitrary dose or concentration of the bronchoconstrictor agent used. By choosing a histamine dose as low as 1 μmol (325 μg), Duiverman and colleagues found very few responders both in the uncomplicated preterm survivors and in the group with bronchopulmonary dysplasia. At such a dose, only those who had a degree of airway responsiveness comparable with clinical asthma would be identified. One can only infer from their study that long term survivors of bronchopulmonary dysplasia were no more likely than other children of preterm birth to have a degree of airway responsiveness as severe as that of the asthmatics. Moreover, with very few positive airway responders in a small study group it would be difficult to show a significant difference statistically, even if such a difference had existed. Additionally, without a reference population, they cannot say whether their findings were normal or abnormal.

In our own study of a cohort of low birthweight children we found that the distribution of a positive airway response to histamine formed a continuum.[3] At very low doses of histamine very few subjects in either the low birthweight cohort or a reference group showed a positive airway response. On the other hand, a significantly greater proportion of low birthweight children had a positive airway response, at moderate histamine doses, suggesting a shift in the frequency distribution of airway responsiveness. Children with bronchopulmonary dysplasia were slightly more responsive than other low birthweight children.

We agree with the findings of Duiverman and colleagues that very few children with bronchopulmonary dysplasia have a degree of airway responsiveness to histamine similar to recognised asthmatic subjects. Many do, however, show a mild to moderate increase in airway responsiveness when compared with an appropriate reference population. We are therefore unable to agree with their conclusion that 'bronchial responsiveness to histamine in these subjects (bronchopulmonary dysplasia survivors) was normal'.

References

[1] Duiverman EJ, den Boer JA, Roorda RJ, *et al.* Lung function and bronchial responsiveness measured by forced oscillometry after bronchopulmonary dysplasia. *Arch Dis Child* 1988;**63:** 727–32.

[2] Ahrens P, Zielm S, Strover B, *et al.* Long-term pulmonary and allergic outcome of very low birthweight prematures with and without BPD. *Eur J Respir Dis* 1988;**1**(suppl 1):7S.

[3] Chan KN, Noble-Jamieson CM, Elliman A, *et al.* Airway responsiveness in low birthweight children and their mothers. *Arch Dis Child* 1988;**63:**905–10.

K N Chan *and* M Silverman
Department of Child Health,
Royal Postgraduate Medical School,
Hammersmith Hospital,
Du Cane Road,
London W12 0HS

Maternal narcotic abuse and neonatal thrombocytosis

Sir,

We read with interest the recent report by AlRoomi *et al* on maternal narcotic abuse and its effects on newborn infants.[1] We wish to draw attention to an additional complication, not mentioned in this report, but first regarded by Burstein *et al* in 1979.[2] These authors noted significant thrombocytosis in a prospective study of 33 infants of mothers using narcotic drugs. They also speculated that platelet microaggregates in these babies may give rise to cerebral infarcts. We have recently seen this complication in two preterm infants admitted to the neonatal intensive care unit. Both mothers were registered heroin addicts on a methadone maintenance programme during pregnancy, and at least one was still using heroin regularly.

Case reports

CASE 1

A boy, weighing 2320 g, gestational age 31 weeks, had a normal platelet count until day nine when it began to rise reaching an initial peak of 838×10^9/l in the third week of life and a second peak of 919×10^9/l in the sixth week of life. Other than the mother's substance abuse, there had been no particular antenatal problems and the baby's condition at birth was excellent. On day 4 cranial ultrasound examination showed a periventricular flare, which surprisingly persisted. Cystic degeneration then occurred and at 6 months of age the child had spastic quadriplegia and developmental delay.

CASE 2

A boy, weighing 2280 g, gestational age 32 weeks, had a platelet count which rose from 721×10^9/l at the end of the second week to a peak of 969×10^9/l on the fourth week and at the time of discharge, at 8 weeks, was still 818×10^9/l. This baby showed normal growth and appropriate development at follow up to 1 year of age.

In neither baby were there other abnormal haematological indices. Neither baby had perinatal asphyxia but both showed clinical features of narcotic withdrawal in the early neonatal period. Neither infant had received any antiplatelet drugs. Review of cumulative haematology reports of all other babies admitted to the intensive care unit at this time showed that thrombocytosis of this degree was not present in any infants of non drug abusing mothers during the same period of time.

The periventricular leukomalacia in case 1 was unexpected and it must be considered that the thrombocytosis contributed to the ultimate cerebral atrophy. The true incidence of thrombocytosis in babies of narcotic addicted mothers is unknown as not all babies require admission to a neonatal intensive care unit and only in those who have serial full blood examinations over several weeks is this essentially asymptomatic abnormality revealed.

References

[1] AlRoomi LG, Davidson J, Evans TJ, Falea P, Howat R. Maternal narcotic abuse and the newborn. *Arch Dis Child* 1988;**63:**81–3.

[2] Burstein Y, Giardina PJV, Rausen AR, Kandall SR, Siljestrom K, Peterson CM. Thrombocytosis and increased circulating platelet aggregates in newborn infants of polydrug users. *J Pediatr* 1979;**94:**6.

H M Chambers *and* R R Haslam
Departments of Pathology and Neonatology,
Queen Victoria Hospital,
Adelaide, Australia

Intracranial pressure monitoring in a group of critically ill children

Sir,

The article by Tasker *et al* describes their experience of intracranial pressure monitoring in a heterogeneous group of critically ill children.[1] While agreeing with the principle of early intervention we wish to make several points.

Using almost exclusively the intraventricular catheter method of monitoring intracranial pressure described by McWilliam and Stephenson[2,3] we have managed 48 children aged 7 weeks to 13 years with a variety of disorders over the past five years (table).

Table *Details of the 48 children managed*

I	**Infectious and parainfectious illness**	
	Meningococcal disease	9
	Pneumococcal meningitis	4
	Haemophilus influenzae meningitis	2
	Measles encephalitis	1
	Mycoplasma encephalitis	1
	Epstein-Barr virus encephalitis	1*
	Parainfectious encephalopathy	1
II	**Metabolic illness**	
	Reye's syndrome ('idiopathic')	17
	Medium chain acyl CoA dehydrogenase deficiency	1
	Ornithine transcarbamylase deficiency	1
	Diabetic hyperosmolar coma	1
III	**Hypoxic ischaemic encephalopathy**	
	Sudden infant death syndrome, postcardiac arrest	2
	Hydrocephalus, postrespiratory arrest	1
IV	**Haemolytic uraemic syndrome**	1
V	**Haemorrhagic shock encephalopathy**	2
VI	**Miscellaneous**	
	Brain stem astrocytoma	1
	Unexplained encephalopathy	1
	Pseudomembranous colitis with septic shock	1
	Total	48

*Failed technique.

Our technique for intraventricular pressure monitoring is simple and can be done by the physician at the bedside. In only one case did monitoring fail (failure rate 2%). There was one case of secondary sepsis and no long term sequelae. There were no intracerebral haemorrhages. The only major difference in our management from that of the authors was that we used continuous infusions of morphine and pancuronium rather than bolus doses.

Twenty seven of our patients had a good or moderate neurological outcome and four were severely handicapped using the Seshia scale of assessment.[4] Seventeen patients died. These results are very similar to those of the authors. The average cerebral perfusion pressure of our normal survivors, however, was 36·5 mm Hg, and nine of these 18 normal survivors had minimum cerebral perfusion pressure of less than 40 mm Hg. The duration of the minimum cerebral perfusion pressure could not be assessed as only hourly observations were charted by the nursing staff (in addition to the acute changes in cerebral perfusion pressure). Three of the 17 who died had a minimum cerebral perfusion pressure of greater than 45 mm Hg, but the average minimum of those who died was 20·7 mm Hg.

The difference was significant (p less than 0·05 by paired *t* test). In contrast with the authors' experience a child with Reye's syndrome who had maximum intracranial pressure of 65 mm Hg survived to be normal. Eight of our survivors had a Glasgow coma scale of less than 5 (not attributable to drugs) before monitoring of intracranial pressure.

There are several areas of intracranial pressure monitoring which need further clarification. The question of what is an adequate cerebral perfusion pressure has yet to be resolved. Factors such as regional blood flow variation, duration of minimum cerebral perfusion pressure, and the underlying disease process may be of great importance.

We feel that taking a cerebral perfusion pressure of 40 mm Hg as a cut off point without regard to the underlying illness and the duration of that pressure is at present wrong, and that more prospective research is needed in this area. Further, with our experience we would suggest that a Glasgow coma scale at less than 5 is not necessarily an indicator of a poor outcome. Therefore, neither of these parameters should necessarily be used to decide on the initiation or continuation of a treatment.

Finally, it is not clear how many of the patients of Tasker *et al* were transferred from other hospitals before the institution of neurointensive care. Over the past six months we have provided an intensive care transport service for critically ill children. During that period we have been asked to transport four children in whom the intracranial pressure was definitely raised or impaired cerebral perfusion pressure was suspected. In all cases the children were assessed by one of the authors and measures taken to reduce intracranial pressure and to stabilise mean arterial pressure before transfer from the referring hospital. We feel that in this way fluctuations in cerebral perfusion pressure may be minimised. Identifying illnesses in which cerebral perfusion pressure is significantly reduced and developing scoring systems allowing timely intervention may minimise later handicap.

References

[1] Tasker RC, Matthew DJ, Helms P, Dinwiddie R, Boyd S. Monitoring in non-traumatic coma. Part I: invasive intracranial measurements. *Arch Dis Child* 1988;**63**:888–94.

[2] McWilliam RC, Stephenson JBP. Rapid bedside technique for intracranial pressure monitoring. *Lancet* 1984;**ii**:73–5.

[3] McWilliam RC, Stephenson JBP. Bedside intracranial pressure monitoring. *Lancet* 1985;**ii**:341.

[4] Seshia SS, Seschia MMK, Sachdeva RK. Coma in childhood. *Dev Med Child Neurol* 1977;**19**:614–28.

G Balakrishnan, C H Skeoch, J B P Stephenson,
R C McWilliam, D Hallworth, *and* J F Sinclair
Royal Hospital for Sick Children,
Yorkhill, Glasgow G3 8SJ

Validity of forced expiratory flow volume loops in neonates

Sir,

Despite the comments of LeSouëf and Landau on our methodology in the *Archives*,[1] we remain concerned about the validity of forced expiratory flow volume loops in neonates.[2] We initially examined the effects of compression pressures ranging from 1·0 to 4·5 kPa and found that pressures above 3 kPa did not lead to significantly higher flows of functional residual capacities in our normal healthy full term babies. We are not competent to comment on what pressures should be used in older infants with airways obstruction but are worried rather than reassured that there is no single pressure which can be used for all infants. It is, presumably, necessary to study each infant over a wide range of compression pressures in order to detect the optimal. Presumably any effective therapeutic manoeuvre could alter the lung mechanical characteristics of the respiratory system to such an extent that this pressure no longer applied, so that the full range of pressures would again have to be used, making this a very difficult and cumbersome technique to use in practice.

We are also concerned that there appear to have been only three previous measurements on the transmission of the pressure to the pleural space.[3] The authors, Taussig *et al*, found that only 25% of the applied pressure was transferred, a surprisingly low figure when all previous measurements have suggested that the chest wall is far more compliant than the lung in the neonatal period. These figures do, however, fit in well with our own conclusions that the baby is making inspiratory efforts from soon after the onset of the compression pressure and, indeed, analysis of our traces has shown that on all occasions the oesophageal pressure had fallen from its peak value before the functional residual capacity point had been reached in the 188 squeezes. As the transfer pressure is so small, we also think it unlikely that the supramaximal flows for squeezes applied during expiration are caused by flow transcience from compression of the gas in the large airways as claimed by LeSouëf and Landau.

In summary, we are not claiming that this technique is without value but are concerned that the measurements obtained often do not represent flow limitation. This will inevitably considerably reduce sensitivity and may affect the interpretation given on changes (or lack of changes) occurring after therapeutic manoeuvres.

References

[1] LeSouëf PN, Landau LI. Validity of forced expiratory flow volume loops in neonates. *Arch Dis Child* 1988;**63**:450–1.

[2] Hoskyns EW, Milner AD, Hopkin IE. Validity of forced expiratory flow volume loops in neonates. *Arch Dis Child* 1987;**62**:895–900.

[3] Taussig LM, Landau LI, Godfrey S, Arad I. Determinants of forced expiratory flow in newborn infants. *J Appl Physiol* 1982;**15**:1270–7.

E W Hoskyns, A D Milner, *and* I E Hopkin
Department of Child Health,
University Hospital,
Queens Medical Centre,
Nottingham NG7 2UH

Comparison of five tests used in diagnosis of neonatal bacteraemia

Sir,

We have read with interest the paper by Kite *et al.*[1] The authors have obtained the best sensitivity (61·8%), specificity (90·3%), and positive predictive accuracy (56·8%) using a combination of the acridine orange leucocyte cytospin test, C reactive protein assay, and nitroblue tetrazolium test. Moreover, they have showed improvement of the sensitivity (92·3%) excluding bacteraemia with coagulase negative staphylococci (21/34 episodes of bacteraemia). Unfortunately, the authors have not pointed out the negative predictive accuracy of the evaluated tests—that is, the probability that sepsis is not present if the tests are negative.

Recently, we have evaluated the usefulness of seven tests (neutrophil blood cell count, the ratio of band forms to total neutrophils, the platelet count, and the quantitative determination of serum IgM, C reactive protein, alpha-I-acidglycoprotein, and haptoglobin) for the early identification of the serious neonatal infections.[2] We have prospectively studied 70 preterm newborns: 15 with sepsis, two with serious infections without bacteraemia, and 53 without infections. When two or more tests were positive, sensitivity was 76·4%, specificity was 83%, positive predictive accuracy was 59%, and the negative predictive accuracy was 91·6%.

Previously, Philip and Hewitt have reported (using band/total neutrophils, leucocyte count, latex C reactive protein, erythrocyte sedimentation rate, and latex haptoglobin) that, when two or more tests were positive, the positive predictive accuracy was 39% (62% considering 'very probable' sepsis); on the other hand, when less than two tests were positive, the probability that sepsis was not present was 99% (negative predictive accuracy).[3]

In our opinion, values of positive predictive accuracy as 56·8%,[1] 59%,[2] or 39–62%[3] are unacceptable in predicting a severe disease as neonatal sepsis. On the contrary, we want to underline the great potential usefulness of the negative predictive accuracy of the evaluated tests[2 3] to exclude infection and avoid antibiotics when the diagnosis of sepsis on clinical grounds is doubtful.

References

[1] Kite P, Millar MR, Gorham P, Congdon P. Comparison of five tests used in diagnosis of neonatal bacteraemia. *Arch Dis Child* 1988;**63**:639–43.

[2] Stabile A, Pastore M, Romanelli V, Miceli Sopo S, Flamini G, Pesaresi A. Diagnosi precoce di sepsi nel neonato pretermine. *Pediatr Med Chir* 1987;**9**:3–4.

[3] Philip AGS, Hewitt JR. Early diagnosis of neonatal sepsis. *Pediatrics* 1980;**65**:1036–41.

S Miceli Sopo, M A Pesaresi,
M Pastore, *and* A Stabile
Clinica Pediatrica dell'Università
Cattolica del Sacro Cuore,
Largo Gemelli 8, 00168,
Roma, Italy

Sir,

We read with interest the paper by Kite *et al.*[1] We would like to present our experience with C reactive protein, which we have been using for the past five years in combination with haematological tests (that is, abnormality observed in any of the following: total white cell and/or neutrophil counts, immature to total neutrophil ratio) for the diagnosis of neonatal infection. Estimations of C reactive protein were originally performed manually by latex agglutination test but later quantitatively by an automated analyser employing immunoturbidometry. The overall sensitivity of the initial C reactive protein in 'proven' neonatal infections (that is, positive blood and/or cerebrospinal fluid cultures) in over 200 such cases was 74%. In infections occurring in the first 24 hours it was lower (60%). When these results were broken down according to the isolated organism the sensitivity was 100% for fungal, 95% for Gram negative, but only 55% for Gram positive infections, respectively. This was due to low sensitivity not only to coagulase negative staphylococci (25%) but to *Staphylococcus aureus* (48%) while the sensitivity for other Gram positive cocci was higher. In infections due to *S aureus*, however, where the initial concentration of C reactive protein was low, it increased within one to three days of the diagnosis. With these staphylococcal infections the other haematological tests mentioned above gave greater sensitivity (71%). When C reactive protein was considered in combination with the haematological tests the overall sensitivity increased to over 95% (that is, neonates having at least one test abnormal). The concentration of C reactive protein was of little value in operated neonates with suspected sepsis and it was also falsely raised in the presence of significant perinatal asphyxia (although in both instances there was a falling trend in serial measurements). Using serial measurements of C reactive protein as a guide to successful antibiotic treatment we have been able to reduce the length of treatment and the number of neonates receiving antibiotics for over seven days as in our experience in most cases C reactive protein values became normal first, compared with the white cell count and differential. In our unit, however, the combined use of C reactive protein and haematological tests has not led to any significant reduction in the number of neonates being put on antibiotics.

Reference

[1] Kite P, Millar MR, Gorham P, Congdon P. Comparison of five tests used in diagnosis of neonatal bacteraemia. *Arch Dis Child* 1988;**63**:639–43.

H D DELLAGRAMMATICAS,
T TAPRATZI, *and*
G KOURAKIS
Neonatal Intensive Care Unit,
2nd Department of Paediatrics,
University of Athens, Athens,
Greece 11527

Renal failure in the newly born

Sir,

Dr Brocklebank states that a bicarbonate dialysis solution would be preferred to the standard lactate solutions in some infants.[1] Bicarbonate dialysis solutions are not manufactured commercially but can be prepared by the hospital pharmacist. We have not yet administered them to neonates but have used them in older infants and children in renal failure after cardiac surgery.

We use two solutions formulated to contain sodium and glucose concentrations similar to standard dialysis solutions (for example, Dianeal, Baxter Healthcare Ltd) (table).

Table *Two solutions used for bicarbonate dialysis*

	Bicarbonate solution	*Low sodium bicarbonate solution*
Glucose, anhydrous	30 g/l	30 g/l
Sodium	140 mmol/l	130 mmol/l
Chloride	90 mmol/l	80 mmol/l
Bicarbonate	50 mmol/l	50 mmol/l

A basic solution containing glucose and sodium chloride in 950 ml of water is heat sterilised in glass containers and can be prepared in advance; 50 ml sodium bicarbonate 8·4% injection (IMS Ltd) is added immediately before use to complete the solution. Calcium and magnesium salts are not present in the bicarbonate dialysis solutions and may need to be supplemented by the intravenous route.

Further information on the solutions and their preparation are available from one of the authors (AJN).

Reference

[1] Brocklebank JT. Renal failure in the newly born. *Arch Dis Child* 1988;**63**:991–4.

A J NUNN *and* T MCKENDRICK
Royal Liverpool Children's Hospital,
Alder Hey, Eaton Road,
Liverpool L12 2AP

Prone or supine?

Sir,

Recently considerable interest has been shown in the question of whether babies should be nursed prone or supine.[1-4] We feel that a word of caution should be added to the suggestions that it may be better to nurse preterm babies in the prone rather than in the supine position. We have seen two babies with notching of the alar margin seemingly caused by pressure from a nasal endotracheal tube.

One child was born at 30 weeks' gestation, was ventilated for 11 days, and developed a notch of her left nostril. The other child was born after a gestation said to be 23 weeks, was intubated for 53 days, and also developed a notch of the left nostril (figure). Both children have required reconstructive surgery.

We feel that the most likely explanation is that these defects were caused by pressure from a nasal endotracheal tube producing ischaemic necrosis of the alar margin. Although this could happen whatever position the baby is nursed in, it is most likely to occur in a baby nursed prone when the endotracheal tube and its connections may be pushed upwards or to one side. Also the situation is more likely to pass unnoticed in this position. Both these children came from a special care baby unit where babies are commonly nursed prone for much of the time.

Reconstructive surgery for this defect is difficult. If the prone position is used for babies with nasal endotracheal tubes perhaps an awareness of this problem coupled with supporting the baby's shoulders on a small pillow or roll would lead to fewer injuries.

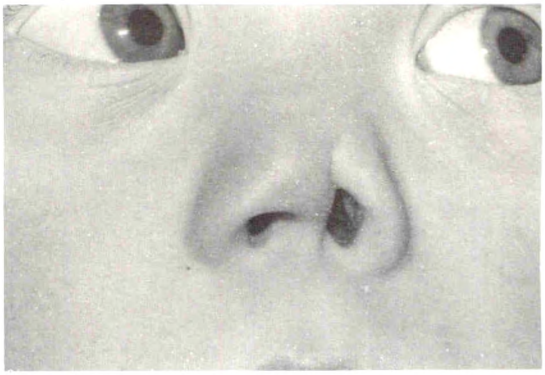


Figure *Child showing notch in left nostril.*

References

[1] Anonymous. Prone or supine for preterm babies? *Lancet* 1988;**i:**688.

[2] Wagaman MJ, Shutack JG, Moomjian AS, Schwartz JG, Shaffer TH, Fox WW. Improved oxygenation and lung compliance with prone positioning of neonates. *J Pediatr* 1979; **94:**787–91.

[3] Martin RJ, Herrell N, Rubin D, Fanaroff A. Effect of supine and prone position on arterial oxygen tension in the preterm infant. *Pediatrics* 1979;**63:**528–31.

[4] Masterson J, Zucker C, Schultze K. Prone and supine positioning effects on energy expenditure and behaviour of low birth weight neonates. *Pediatrics* 1987;**80:**689–92.

R J Bray, T A Piggot, *and* C A Reid
Departments of Anaesthesia and
Plastic and Reconstructive Surgery,
Royal Victoria Infirmary,
Newcastle upon Tyne NE1 4LP

Archives of Disease in Childhood, 1989, **64,** 431–438

Spring books

Personal choice *D P Addy*

Ten past ten. Cold night. November. Nursing 'flu. Telephone. The editor. Wants to start a new kind of book review. Will I write about books I've bought, begged, received or otherwise acquired in the last few months, years, or, indeed, ever? (He actually said the last five years but I've never understood why author's licence should be restricted to poets.) What use have I made of them?

Well, I don't often buy textbooks. If all the sellers of medical textbooks kept in business by the personal spending of people like me were to be counted, there wouldn't be enough to form one half of a boxing match. I did, as an act of loyalty to the cause, buy the BPA Diamond Jubilee book *Child Health in a Changing Society* but at the risk of being court martialled by the BPA Council, I must admit that I haven't enjoyed it as much as Dick Smithells did. The books I do buy are often not work books and therefore not useful in that sense. I bought the new American reprint of the 1892 edition of Osler's *Principles and Practice of Medicine* which looks very smart on my bookshelf alongside Harvey Cushing's *Life of Osler* and makes an interesting 'dip-in' from time to time. Did you know, for instance, that Osler referred to typical breath holding attacks under the heading Spasmodic Laryngitis and confused it with the laryngeal spasms of rachitic tetany? His recommended treatment for difficult cases was a warm bath several times a day during which the back and chest was to be thoroughly sponged for a minute or two with cold water. During an attack, though, the cold water was better 'dashed into the child's face'. How often the first remedy led to a need for the second, he did not say.

A few Christmases ago my wife gave me the Keynes Press issue of William Pickles' beautiful little book *Epidemiology in a Country Practice.* Now there's a real gem of a book if ever there was one; general practice and genuine research in Wensleydale in the 1930s; a sort of intellectual, up market, medical James Herriot. Its main usefulness is to be lent to friends for their holiday delight.

Apart from the usual memory jogging and dose checking pocket books, one of the books I refer to most is Professor Peter Harper's *Practical Genetic Counselling* which I find extremely useful for checking modes of inheritance and the sort of simple genetic counselling I feel able to do without reference to a geneticist. My own particular clinical interests lead me to refer fairly frequently to Edward Brett's *Paediatric Neurology* and to Swaiman and Wright's now aging two volume *Practice of Pediatric Neurology.*

The editor told me that one of his favourites has been Niall O'Donohoe's *Epilepsies of Childhood* and I too have had more than my money's-worth out of it over the years. The books on epilepsy I now find most invaluable are *Epileptic Syndromes in Infancy, Childhood, and Adolescence* by Roger, Dravet, Bureau, Dreifus, and Wolf, which I was given, and Jean Aicardi's *Epilepsy in Children* which I bought. I wouldn't like to try to manage without either of them now.

I have an almost continuous series of *Yearbooks of Pediatrics* going back to 1959. I find them useful for reference, though I no longer read each new edition quite as assiduously as I used to. The inclusion of a cumulative five year index in the 1987 Yearbook was very useful and is an idea well worth the consideration of other publications. Another extremely valuable quick reference source is, of course, the annual bibliography of *Developmental Medicine and Child Neurology.*

The only general paediatric textbook I've ever owned is Sir Wilfrid Sheldon's *Diseases of Infancy and Childhood* which I bought as a student. I refer as necessary to the usual British and American multiauthor tomes in the hospital library and I subscribe to the *BMJ, Archives, Developmental Medicine and Child Neurology,* and *Epilepsia.*

It's just struck me that there are a lot of books on my shelves that I never use. 'Books that are no earthly use to anybody' would certainly be a novel book review section, but we mustn't be too hard on authors, they're a hard working bunch and we reap as we sow.

Human Growth—A Comprehensive Treatise. Vol 1, 2, and 3. By Frank Falkner and JM Tanner. 2nd Ed. Pp 496, 555, and 552: $83·40, $90·00, and $90·00 hardback. Plenum Press, 1986. ISBN 0306–419513, 0306–419521, and 0306–41953X.

The second edition of this 'comprehensive treatise' in three volumes has 18 new chapters (13 on subjects not in the first edition) but omits the previous long historical chapter now covered admirably in Tanner's *History of the Study of Human Growth*. The first volume entitled *Developmental Biology and Prenatal Growth* concentrates on many aspects of fetal and embryonic growth, including the physiology, biochemistry, pharmacology, endocrinology, and immunity, but extends into the postnatal period with the last two subjects and also with the sections on the outcome for low birthweight infants. The first section of volume 2, entitled 'Postnatal Growth', describes growth processes at various stages of development, including bone and dental growth, body composition and endocrine aspects. The second half, entitled 'Neurobiology' may be of less general interest, concentrating on fetal and neonatal neurological development in terms of histology and function. The first five chapters of volume 3, entitled 'Methodology', describe in detail techniques of postnatal anthropometry (fetal being in volume 1) and how to use and analyse data for individuals, growth studies, and standards. The chapters that follow cover the genetics of growth, including twins, and growth in relation to environment and secular changes.

The editors describe these volumes as being useful to paediatricians, human biologists, and all concerned with child health, and to biometrists, physiologists, and biochemists working in the field of growth. It is important, however, for potential readers and purchasers to be aware that these unique comprehensive books cover the morphological, physiological, and theoretical aspects of human growth, and as such are excellent, but they are not intended to present a clinical account of growth disorders, nor do they present growth charts and standards and cannot serve as reference manuals for these.

With contributions from 84 authors, the editors are to be congratulated on compiling these volumes so admirably without dictating style. Inevitably, however, there is a lack of consistency in the form and depth of the chapters, and there is a certain amount of overlap and repetition—for example, the growth outcome for low birthweight infants and the age of menarche in different populations each appear in three different places. One can appreciate how difficult it would be to cross reference within the manual itself, but the reference lists at the end of each individual chapter are very comprehensive. Unfortunately the reader, who may not relish purchasing all three volumes, may find difficulty in locating some subjects of interest to them, as the volumes, which are separately indexed, have titles and subtitles that are not always an adequate guide.

Some subjects covered, such as certain 'disease processes', one would not anticipate, but these are presumably included because they throw light on the normal mechanisms of growth. Examples of these are clinical disorders of sexual development in relation to neuroendocrine control of puberty and the effect on growth of chromosomal anomalies, with descriptions of the associated clinical features. In contrast, certain subjects are dealt with in surprisingly little depth. There is a strong emphasis in these volumes on the fetus, perinatal period, and infancy (occupying over half the total contents), but much less on certain aspects in older children such as the later development of neurological function and behaviour, the effects of malnutrition in the long term, and the size of various organs and tissues postnatally. Though the effects of different social backgrounds are well considered, I was surprised to find little reference to psychosocial or emotional deprivation and abuse, which are so evident and important in present day society, whereas an entire and excellent chapter is devoted to physical activity and growth in the child.

These criticisms are, however, trivial compared with my overall very favourable impression of these books and I can certainly recommend their purchase, particularly for appropriate libraries.

J M H Buckler
CONSULTANT PAEDIATRICIAN
University Department of Paediatrics and Child Health, Leeds General Infirmary

CICT: Pediatric Body CT. Vol 10. Edited by MJ Siegel. Pp 286: £47·50 hardback. Churchill Livingstone, 1988. ISBN 0443–085331.

Paediatricians whose clinical work dictates a high degree of dependence on diagnostic imaging will find this book useful, dependent, and well referenced. There is comprehensive coverage of the major organs with the exception of the nervous system interesting chapters on quantitative computer tomography and ultrafast computed tomography add a delightful update.

As imaging involves many modalities those chapters that compare imaging methods and therefore maintain a good perspective are welcomed but are unfortunately few. Many chapters hardly acknowledge the clinical perspective of the use of computed tomography but no book is without its faults.

The illustrations are of high quality and the legends on the whole are appropriate Apart from covering all the organs in the abdomen and chest there are in addition chapters specifically devoted to the neck and the muscular skeletal system. These together with the two case studies provide an added completeness to the potential use and at times overuse of computed tomography in paediatrics. The radiation burden of computed tomography fortunately has not been forgotten.

This is a useful book in which the edito has assembled acknowledged experts to write their appropriate chapters. It i essentially dedicated towards radiologist but enthusiastic paediatricians who are happy to look for specific information wil find this book useful.

I Gordon
SENIOR LECTURER IN DIAGNOSTIC
RADIOLOGY
Hospital for Sick Children
London

Disorders of Gastrointestinal Motility in Childhood. Edited by PJ Milla. Pp 143 £21·50 hardback. John Wiley, 1988. ISBN 0 47191780X.

The rapid growth of paediatric gastroenterology has brought with it a number o monographs on various aspects of the subject. The latest is this which brings together 16 contributors from the United Kingdom, United States, and Belgium Together they have produced a text which is clear, comprehensive, and of practica value to the practising paediatric gastroenterologist and general paediatrician.

The text is divided into four main sections The first deals with the ontogeny of gastrointestinal motor activity. This is divided into three main chapters dealing with the development of motor control, intestinal motor activity in the preterm infant, and the development of the lower oesophageal sphincter in the preterm infant. The second section deals with disordered oesophageal function in two chapters. One deals with gastro-oesophageal reflux in infancy. The second deals with reflux and chronic bronchopulmonary disease. The third section covers small intestinal disorders and colonic function in five chapters. The first is on intestinal pseudo-obstruction in childhood. The second on the pathology of this condition. The third on motility disorders in cystic fibrosis. The fourth on the irritable bowel syndrome, and the last on constipation. The final section covers therapeutics and the use of prokinetic agents.

Despite its multiauthorship Peter Milla has achieved a cohesiveness of style, clarity, and brevity. Each chapter has useful references. It is inevitable that there will be a slight degree of overlap between different authors but this is a minor fault in a book that should be useful in the understanding and management of this difficult area of paediatric gastroenterology. It should find a useful place in the libraries of general paediatricians as well as of those working entirely in paediatric gastroenterology.

V Miller
CONSULTANT PAEDIATRIC
GASTROENTEROLOGIST
Booth Hall Children's Hospital,
Manchester

Treatment and Prognosis: Paediatrics. By G S Clayden and R L Hawkins. Pp 370: £17·50 paperback. Heinemann Medical Books, 1988. ISBN 0–433–06010–7.

This volume is one of the *Treatment and Prognosis* series, a multiauthor text edited by Clayden and Hawkins. The remit of the book is to provide a rapid update for these aspects of 'all important diseases of childhood' and this impossible task is valiantly attempted by the editors.

The book is designed for busy paediatricians, those preparing for examinations, and general practitioners desiring information on likely current practice at their specialist centres as well as some indication as to treatment that can be started at home.

Each bodily system is dealt with in a separate chapter, with extra chapters on neonatal disorders and poisoning. There is a fairly consistent format of around a page of text for each individual disease within these systems, starting with a brief description of the condition and followed by numerically arranged treatment options, then paragraphs on prognosis and a plan of follow up. Some authors tend to include suggestions about investigations within the treatment protocols, though this is not generally part of the discussion. The lack of information on pathophysiology, differential diagnosis, and investigation is initially unsettling to one not used to the concept of this series.

It would be easy to criticise the balance of such an ambitious project; the neonatal section is very brief and contains only 20 lines on meconium aspiration syndrome. Pyloric stenosis is not covered at all in the book whereas benign liver tumours receive two pages and dengue one page, respectively. Having said this most chapters are very well conceived and comprehensive, although not all would agree with the opinions of some authors as to first choice treatment.

The book performs best as a source of references for the interested clinician to explore further the 'Treatment and Prognosis' of the commoner, and indeed less common, childhood disorders and can be recommended for this task, although there will always be a need to read further about the other aspects of these conditions.

J K H Wales
LECTURER IN PAEDIATRICS
Sheffield Children's Hospital
Sheffield

Interviewing the Sexually Abused Child. By David PH Jones and Mary G McQuiston. Pp 56: £4·50 paperback. Gaskell, 1988. ISBN 0 902241 23 0.

The publication of this book comes at a most opportune time given the major concerns about both the physical examination and the interview of children suspected to have been sexually abused. This is in fact the third edition of this particular publication in three years, which indicates the speed of change in this area of major concern to many professionals whose interests centre on the potentially sexually abused child, whether they be medical, social workers, or police, because sexual abuse is at the same time a traumatic event with both physical and psychological consequences, a criminal act, and a form of child abuse requiring the possibilities of consideration of care. Because a small proportion of children show unequivocal physical signs it is essential that guides to interviewing be authoratative, and assist those who interview children to conduct both reliable and valued interviews.

David Jones and Mary McQuiston's book begins with an exploration of the predicament of the child sexual abuse victim looking at both the effects and the considerable problems that exist for children in being able to speak at all. They then review important issues for interviewers such as the fact that children are far more reliable as witnesses than was thought previously, and that their memory for central events even in the earlier years of childhood can be excellent. They examine some general principles of good interviewing including comments on the setting, presence of other parents, ways of recording a session, and which professionals should conduct such interviews and their general experience. They give an extensive guide to the interview itself, including a good exploration of language, anxieties, the use of toys and play material including the anatomically correct dolls and various forms of questioning styles and behavioural observation.

There is a good discussion of the use of facilitation which has been recommended in the Cleveland Enquiry Report as being a second stage examination by skilled and experienced interviewers. There is also an important discussion of the process of validation including the introduction of statement validation techniques which have begun to be developed in both Europe and North America.

This is an excellent introduction to the field of interviewing the sexually abused child, and will be of great value to all those professionals whose task it is to compliment the skilful physical examination of children.

A Bentovim
CONSULTANT PSYCHIATRIST
Hospital for Sick Children
London

The Child with Febrile Seizures. By Sheila Wallace. Pp 182: £25 hardback. Wright, 1988.

Unless my mathematics is seriously flawed, the febrile convulsion rate in England and Wales is about one child every half hour. It is hardly surprising, therefore, that the subject is one which continues to provide for paediatricians both employment and cerebral exercise. One of those whose cerebrum has been most exercised in this way over the last 20 years is the author of this book which completes a quadrumvirate of monographs that have contributed to my own education on the subject over the years,[1–3] the foundation of my interest having been Dr Lennox-Buchthal's little gem which must surely stand as a medical classic.

Dr Wallace has produced a detailed, thoughtful, scholarly, comprehensive, and up to date review of the subject. Of the 412 references, 160 are to publications in the present decade (14 are pre-1900 and 10 pre-1750l). Some indication of the extent of the author's own contribution to the subject is given by the fact that some 25 of the references are to her own publications. It is doubtful, though, whether 'unpublished data' and 'presented to the Annual Meeting of the . . . . Association' should have found their way into the list of references.

The main message of the book is that 'the child who presents with a febrile seizure is providing an acute indication that all may not be well with his/her nervous system'. Evidence is presented that febrile convulsions are commonly associated with neurological abnormality. As regards major neurological problems, this association largely results from the all embracing definition of febrile seizures as 'any seizure of cerebral origin which occurs in association with any feverish illness'. Such a definition, while perfectly logical, leads, if unqualified, to ridiculous assertions such as that the death rate from febrile seizures has been as high as 11%. This statistic derives from a study of children who convulsed before dying of infection in the preantibiotic era and is obviously irrelevant to the subject of febrile convulsions as understood today. I do not myself subscribe to the doom and gloom school on this subject and I have yet to be convinced that a child who is apparently well after a febrile convulsion is likely to benefit from a surfeit of medical concern.

This is an important book presenting the personal view of an expert on the subject whose own contribution demands that her view be considered seriously and respected, even though one may not agree with it in every detail.

References

[1] Millichap JG. *Febrile convulsions.* New York: Macmillan, 1968.

[2] Lennox-Buchthal MA. Febrile convulsions. A reappraisal. *Electroencephalogr Clin Neurophysiol* 1973 supplement 32.

[3] Nelson KB, Ellenberg JH. *Febrile seizures.* New York: Raven, 1981.

D P ADDY
CONSULTANT PAEDIATRICIAN
Dudley Road Hospital,
Birmingham

The Neuropathology of Temporal Lobe Epilepsy. By C J Bruton. Pp 158: £20 hardback. Maudsley Monographs No 31. Oxford University Press, 1988. ISBN 0-19-712155-1.

This is a description of clinical and pathological findings in 249 patients who underwent anterior temporal lobectomy at the hands of one surgeon over a 25 year period. The criteria for surgical intervention were frequent fits, inadequately controlled by drugs; focal, unilateral temporal lobe spike discharges on electroencephalography; no radiological evidence of tumour and IQ greater than 70. Most specimens of temporal lobes were examined in a systematic fashion and cases classified on the basis of histopathological findings within the resected lobe. The diagnostic criteria of each group are clearly described; clinical correlations and outcome are discussed within each diagnostic group. The volume is completed by a short conclusion which compares the benefits of surgery between groups, the bibliography, and appendices tabulating clinical details of all patients.

The format of the book is attractive and the style makes it easy to read. The quality of illustrations is good but I would have liked to see more photomicrographs to illustrate the range of abnormalities in the 'alien tissue' and 'indefinite' groups, not difficult to arrange as there are five blank half pages in the appropriate chapter. I found the term 'alien tissue lesion' inappropriate. The lesions described under this heading are ones which most pathologists would term hamartomata; they comprised glia, neurones, and blood vessels, all structures which one would expect to find in the cerebral cortex. Clinical details were brief and I think that most paediatricians would want to know more about outcome than frequency of fits and merely a comparison with preoperative state under the heading 'personality and social adjustment'.

Although the onset of symptoms in two thirds of cases was during infancy or childhood, the subjects of this book are a small carefully selected group of patients, quite unrepresentative of children in whom a diagnosis of epilepsy is made. For this reason I cannot recommend this book fo purchase by individual paediatricians despite its modest price. I even hesitate t recommend it for the bookshelf of the paediatric neurologist but would, rather draw it to his attention and suggest that h persuades his neurology or neuropatholog department to buy it so that he may consul it from time to time.

J W KEELIN
CONSULTANT PAEDIATRIC PATHOLOGIS
John Radcliffe Hospital
Oxfor

A Textbook of Epilepsy. Edited by J Laidlaw A Richens, and J Oxley. Pp 644: £6 hardback. Churchill Livingstone, 1988.

In view of the fact that if you claim an interest at all in epilepsy you will undoubtedly already have ready access to on of the first two editions of *A Textbook o Epilepsy,* you may ask why you, or you library, should spend £60 on the new one The answer is that it has been very extensively rewritten and updated. When the book first appeared in 1976 there were 1 contributors. For the second edition i 1982 there were 37 and now there are 30 Twenty two of the contributors to the second edition have now bowed out an there are 15 new names. Only seven of th contributors to the first edition have survived to the third. In bringing out a new edition every six years and making sweeping changes in the authors, the editors obviously intend to keep the textbook alive and on its toes. Dr Oxley has joined the origina editors with the intention of 'supervising further editions well into the 21st century'.

The chapter on childhood epilepsy which in the second edition had thre authors, has now been written entirely by Sheila Wallace. Her chapter is a scholarly discourse strong on description of seizur types and on neurobiology and pathology and pathophysiology and perhaps les strong on a clinical approach to the problems of children with epilepsy and their nonmedicinal management. As might be expected, the chapter contains a comprehensive account of febrile convulsions, thoug the simplistic definition of a febrile convulsion as 'any seizure occurring in associatio with any febrile illness' seems to me unworkable without further qualification. The chapter ends with a list of over 25

PEDIATRIC TITLES FROM APPLETON & LANGE

ADOLESCENT MEDICINE, 2/E

Adele D. Hofmann
University of California
Donald E. Greydanus
Raymond Blank Children's Hospital, Des Moines

This comprehensive text provides practical information on the health care of people between the ages of 10 and 21. The book is written from an integrated perspective, giving equal weight and measure to biological, psychological, and social class issues. This edition covers a range of areas from; adolescent organ system review to alcohol abuse to adolescent sexual and reproductive concerns. Completely revised and updated, this reference contains an entirely new chapter on eating disorders; the coverage of adolescent reproductive issues has been substantially expanded to include a more thorough discussion of homosexuality, sexual abuse and exploitation; and there is new information on several other important topics.

1989 8385-0751-4 Pa £45.95 $75.85
8385-0075-7 Cl £54.50 $89.70

PEDIATRICS, 18/E

Abraham M. Rudolph
Julien I. E. Hoffman
both of the University of California, San Francisco

Pediatrics contains complete, practical information on the diagnosis, treatment and management of normal and sick children. This classic text includes important new findings on infectious diseases, seizure disorders, preventive medicine, pediatric oncology, inborn errors of metabolism and more. Patient-oriented, the text provides in-depth coverage of patho-physiology and physiology and it features an eminent board of associate editors. The latest information on gastroenterology, psychological development, behaviour, psychiatric disorders and AIDS in children. Completely redesigned, the text is highly readable and includes new and expanded charts, graphs and full-colour illustrations. In addition, a greatly expanded drug list forms a new, separate appendix.

1987 8385-7798-9 Cl £42.00 $69.00
Appleton International Edition

HANDBOOK OF PEDIATRICS, 15/E

Henry K. Silver et al
University of California School of Medicine

A current and reliable source of information on the care of children from infancy through adolescence. This excellent reference features tables and figures condensing information and providing concise descriptions of diseases, disorders and diagnostic procedures.

1987 8385-3635-2 Pa £14.70 $23.95
A Lange Medical Publication

For further information on other Appleton & Lange medical titles contact Jean Walmsley at the address below.

APPLETON & LANGE
SIMON & SCHUSTER INTERNATIONAL GROUP
66 Wood Lane End, Hemel Hempstead, Hertfordshire HP2 4RG, England

Prices are correct at time of going to press but may be subject to change.

Sudden Infant Death Syndrome

Edited by JAN L CULBERTSON, HENRY F KROUS and R DEBRA BENDELL

With 12 contributors

The first book to cover both medical and psychological aspects of SIDS, including the medical implications of surviving siblings. Many of the authors are themselves pioneers in the research into SIDS.

January 1989 288 pages illustrated with line diagrams and half tones
£29.95 net hardback 0 340 49381 6

Edward Arnold
A division of Hodder & Stoughton
41 Bedford Square, London WC1B 3DQ Telephone: 01–637 7161

Announcing an important new book from Chapman and Hall Medical

Diseases of the Fetus and Newborn

Pathology, radiology and genetics

Edited by **G B Reed,** *Natividad Medical Center, California, USA,* **A E Claireaux,** *Great Ormond Street Hospital for Sick Children, London, UK,* and the late **A D Bain,** *The Royal Hospital for Sick Children, Edinburgh, UK*

This volume deals with the pathology, radiology and genetics of fetal malformations in considerable detail. The various forms of investigation open to the clinician are described. The book consists of 35 chapters, written by an international team of distinguished authors, and is divided into four parts: Introduction and general disease process; Systemic pathology; Radiology; Medical genetics and prenatal diagnosis.

February 1989 832 pages over 400 illustrations
Hardback 0 412 27990 8 £135.00

For further details please write to Andrea Fox at the address below. The book may be obtained from your usual bookshop. In case of difficulty please write to the Promotion Department at the address below or telephone the Order Department on 0264 332424.

CHAPMAN AND HALL
11 New Fetter Lane, London EC4P 4EE

ferences, many to publications as late as 85.

New to this edition is a chapter on the netics of epilepsy which provides useful formation, though the inclusion of an count of what every schoolboy (or girl) ows about Mendelian inheritance seems appropriate. Also new is a section on ilepsy and mental handicap by John rbett.

Other chapters deal with the problems of ssification, epidemiology, investigations, edical and surgical treatment, neuro- ychiatry, social aspects, and epilepsy in veloping countries.

A Textbook of Epilepsy is by far the most mprehensive and up to date account of ilepsy currently available. Every doctor o regularly cares for people with epilepsy ould have it available for easy and equent reference.

D P Addy
CONSULTANT PAEDIATRICIAN
Dudley Road Hospital,
Birmingham

diatric Behavioural Neurology. Volume Clinical Principles. By C Njiokiktjien. 395: 130 Dutch guilders hardback. Suyi blicaties, 1988. (Distributed by Nedbook , PO Box 3113, 1003 AC Amsterdam, e Netherlands.) ISBN 90–72008–02–2.

aditionally, paediatric neurology and velopmental medicine have concentrated motor and sensory function with prin- les developed from adult function and sfunction. Recent moves towards the erpretation of paediatric problems in ms of neural organisation and behavioural ncepts are the subject of this single hor text. Psychiatric and psychological ncepts sit alongside neuroanatomy and ysiology in a text aimed at a wide dership: paediatric therapists, psycho- ists, and neurologists. Most aspects of diatric neurology are covered, and to ne extent reinterpreted, in varying ounts of detail. A proposed and lengthy ropsychological examination is outlined, owed by an appraisal of aetiological nsiderations. The final bulk of the book nprises consideration of various neuro- avioural disorders. The author is less cessful with conventional neurology n with his interpretation of higher cere- l functions, such as memory and learning, I remain unconvinced by some of his aetiological arguments. There is a very useful and extensive list of 1057 references.

Unfortunately the style is rather ponderous and the occasional reader will find himself confused by the breadth of some of the sections. Part of the problem resides in the poor quality of certain passages, which may relate to the translation from the author's Dutch, but which lack a crispness necessary in such a difficult text.

There is little critical review of the suggested format for examination or testing, or of the literature base which is used to support and expand the text. This didactic approach to so many aspects of neurology does little to encourage me to explore neurobehavioural concepts further, although as a reference text, for exploration of unfamiliar neurological territory, I have found it useful. Much more a library book than one to have on one's bookcase at home.

N Marlow
LECTURER IN CHILD HEALTH
Royal Liverpool Children's Hospital,
Alder Hey, Liverpool

Pediatric Neurosurgery. Theoretical Principles and Art of Surgical Techniques. By AJ Raimondi. With contributions by BA Ishak and ZL Noah. Pp 526: DM 780 hardback. Springer-Verlag, 1987. ISBN 3–540–96408–8.

Is it just nostalgia that makes us think that ours is not an age of great medical personalities? Articles are written in a deadpan style designed to give them that extra coating of veracity, books are sterilised by selecting as many authors as possible and even conferences are likely to attract such numbers that anonymity is the rule rather than the exception. But here is a single author text that exemplifies quite a different, and apparently most unfashionable, approach. Anthony Raimondi, paediatric neurosurgeon for many years in Chicago (although the curious will search in vain for details of his provenance among the title pages of this volume), has written a magnificently personal book that could well be subtitled 'How I perform paediatric neurosurgery'.

It starts with close to 200 pages devoted to the basic technical details of the subjects before spending another 100 pages on tumours alone. These might be tedious even for a beginner were it not for the quality of the illustrations and the startling operative photographs that illuminate the text on almost every page.

If the personality of the author is so exposed in a book then our reaction to what is written will be determined by our personal responses to what the words reveal. Here there is no doubt that one feels in the company of a friend and as with all friendships there are some things to admire and others with which one fervently disagrees. Yet the friendship between author and reader is preserved by recognising that quality of heart whose strengths can survive the most passionate of arguments. And with this volume there is no doubt that (at least to this reviewer's way of thinking, Raimondi's heart is in the right place.

Raimondi demonstrates a brisk disregard for fashion. He suggests, for example, that there are some craniopharyngiomas that cannot be entirely removed (and in whom it would be folly to try). As for untethering the spinal cord, he argues that in some of the dysraphic states the scarring that follows surgery may well produce as much tethering as there was before the operation—a view with which his Chicago colleagues are unlikely to concur.

But is it necessary to have such a book? Do we even need paediatric neurosurgeons? The answer from a country where such a creature as a whole time paediatric surgeon is non-existent (or rather, extinct) would seem to be no, but that is merely to accept our status as a third world nation when advances in health care are being discussed. For the infant (nowadays often premature), the toddler, and the young child all neurosurgical procedures deserve the attention of a specialist, while for children of any age there are some conditions, particularly those related to abnormalities of development, that are seen so rarely in adult practice that they should surely be dealt with by those for whom exclusivity of practice has allowed a wide experience to be gained. At the very least, paediatric neurosurgical cases should be looked after in a paediatric environment, a situation that still does not exist for some units within these islands.

Of course, there should be paediatric neurosurgeons and for them all I recommend this book. For the beginner, the friendly presentation of technical detail will puff away the mystique that always hovers around the neurosurgical world and allow experience to be gained in safety. For those who are already experienced, there is plenty here with which to agree and with which to do battle; the possibility of argument arises on almost every page but behind each printed word one hears the author reminding us with one of the many quotations that his book contains that 'Never have I taught a student archery without, in the end, becoming his target' (Saadi, The Rose Garden, circa 1280 AD).

R HAYWARD
CONSULTANT NEUROSURGEON
Hospital for Sick Children,
London

Vitamins and Minerals in Pregnancy and Lactation. Edited by Heribert Berger. Pp 478: $61·50 hardback. Raven Press, 1988. (Nestlé Nutrition Workshop Series. Vol 16.) ISBN 0–88167–414–1.

The Nestlé Nutrition Workshop series has established a justified reputation for its generally consistent scientific quality. It is unfortunate that this volume does not achieve the same standard. This is because it is devoted to the proceedings of a conference rather than to the customary small and well informed workshop. As a consequence it contains many short presentations and abstracts, a number of which lack the perspective and critical insight that are usually associated with this series.

Nevertheless it would be unfair to dissuade people from using this book merely because it is inconsistent with other volumes in the series. As a 'Conference proceedings' it is of interest and, as such, can certainly be judged to be as good if not better than most such publications. The major reviews and commentaries on personal research are interesting. Among these I would include the contributions by Siimes and by Hallberg on iron metabolism in infants and in pregnant women respectively; that of the late Lucille Hurley and Keen discussing trace element metabolism in pregnancy; and Chiswick's valuable overview of his work on vitamin E supplementation and the risk of periventricular haemorrhage in preterm infants. Others include Delange *et al*'s contribution on iodine nutrition during pregnancy and lactation, in which there is a salutory warning about functional impairment of the thyroid in the infants of mothers given excessive antenatal supplementation with iodine; Pettifor's paper on rickets in infants provides a good overview on this topic and makes a case for this problem to be predominantly that of the very low birthweight infant. Finally there is the particularly thorough review by Kirksey and Rahmanifar on the vitamin and mineral content of preterm human milk. Of these and of the other useful contributions that I have not itemised, most are available in a similar form, often by the same authors, elsewhere. For a general department or reader wanting a relatively painless update on these related aspects of vitamin and mineral nutrition in pregnancy and lactation, however, this would present a useful compilation, as long as they do not resent simultaneously paying for a host of glossy abstracts.

P J AGGETT
SENIOR LECTURER IN CHILD HEALTH AND NUTRITION
Department of Child Health,
University of Aberdeen

The Natural History of Cerebral Palsy. By Bronson Crothers and Richmond S Paine. Pp 270: £18 hardback. Mac Keith Press, 1988.

This exemplary study of Crothers and Paine was first published in 1959 and is now republished as a 'Classic in Developmental Medicine'. In the original study 1800 individuals with cerebral palsy were followed up for some 20 years between 1930 and 1950 and the data provided form the key to lucid and illuminating analyses of what cerebral palsy is and is not, to the study of abnormal and normal motor development, to the variety and evolution of motor disorders that occur in cerebral palsy, and to the very wide range of aetiologies, pathologies, and related disabilities that are associated with neuromotor problems.

First and perhaps foremost this book is a 'good read' and is remarkably undated so far as philosophy and factual presentation are concerned. Thus the information and perspectives contained within it are provided in a fashion that is wholly relevant for a contemporary readership. It is of interest that while we may have come some further way in the last 30 years in our understanding of the causation and epidemiology of cerebral palsies, the excellent chapters on treatment and education are a timely reminder that progress in these areas remains slow and limited.

I suspect that this genuine classic is not as widely known to a readership in the United Kingdom as it should be. This edition can make good that deficit and the book can be confidently recommended fo all paediatricians working in neurology an childhood handicap.

L ROSENBLOO
CONSULTANT PAEDIATRIC NEUROLOGIS
Royal Liverpool Children's Hospi

Essential and Toxic Trace Elements in Human Health and Disease. Edited by A Prasad. Pp 328: $95 hardback. Alan R Lis 1988. ISBN 0–8451–1617–7.

Our knowledge of the role of trace elemen in human health seems to be relat inversely to the profile which these elemen have assumed in public awareness. Ou patchy insight into the metabolism of iro illustrates the ignorance that can persi even when the importance of an eleme has long been appreciated. The situation worse with other trace elements wheth they are essential or not and it is disturbi to see some, such as zinc, selenium, an copper, joining or replacing iron amo the non-specific palliatives of the ther peutic armamentarium. Unquestionab there is a need for a wider appreciation our limited understanding of the toxici and essentiality of many trace elements an of the more subtle early biochemical an clinical effects of their deficiency and tox excess. This book provides such informatio and insight: Prasad has ably compiled th original and review presentations from th inaugural meeting of the Internation Society for Trace Element Research. Co lectively these provide valuable positio papers covering most aspects of the clinica physiological, biochemical, pharmac logical, and toxic actions of trace elements Many papers illustrate the interactions th occur between the trace elements them selves and with other essential nutrient and equally importantly the impact th human disease can have on the system metabolism of trace elements is considere There are some omissions; I could not fin comment on the pathogenic role of copp in Indian childhood cirrhosis.

Advances in trace element research e compass inorganic and clinical biochemi try, physiology, and human disease. Som fascinating areas that are included in th book include the possible role of tra elements in the precipitation and control free radical damage, an appraisal of t role of boron in the metabolism of calciu and magnesium, and a critique of the cas for the essentiality of nickel, silico vanadium, and even arsenic. In general the toxicity of elements was appreciated before heir essentiality, so although the latter elements have only been shown to be necessary for laboratory models their mportance for man may yet be discovered. Human deficiencies of zinc, copper, molybdenum, and selenium have only been proved in the past 20 years, and the contribution on the diverse metabolic roles of manganese suggests that a similar clinical mportance of this element may soon be demonstrated.

Further work on the metabolism of trace elements depends on new approaches including multielemental analytical techniques, the use of low abundance stable sotope tracers rather than radiolabels, and the measurement of proteins that regulate the metabolism of the elements (for example, the role of metallothionein in regulating zinc, copper, and cadmium); all are well described here. These techniques will be needed to solve the perennial problem of how to determine if an individual is at risk of developing a deficiency or toxicity or is actually in such a condition. Certainly anyone who reads these chapters will justifiably become sceptical of claims that simple analyses of hair or plasma are indicative of an individual's trace element status'—whatever that may be.

Readers, irrespective of their degree of experience in this area, would find new nformation, insight, and inspiration from the work presented here, but the book is expensive and it would be best consulted in a library rather than bought personally.

P J Aggett
SENIOR LECTURER IN CHILD HEALTH AND NUTRITION
Department of Child Health, University of Aberdeen

Topics in Pediatric Genetic Pathology. Edited by John M Opitz. Pp 469: $90 hardback. Alan R Liss, 1987. ISBN 0–8451–4242–9.

This volume is subtitled 'The Enid Gilbert-Barness Festschrift', and is a collection of papers by friends and colleagues in honour of Enid Gilbert, a leading contributor to the field of paediatric and genetic pathology. It is also published as a supplement of the *American Journal of Medical Genetics*. Being a Festschrift it has no clear theme and no other declared purpose, but is a pot pourri of papers and reviews loosely embraced by the main title. The book is divided into six sections, the first of which deals with general principles and methods. The chapters on molecular biology applied to prenatal diagnosis and developmental pathology, a review of prenatal death in humans, and papers on midline developmental 'weakness' and neurotomes as the basis of some multiple congenital malformations are of general interest. There is also a useful paper on the differential diagnosis of posterior cervical hygromas in previable fetuses. The second section on developmental effects of aneuploidy and chromosome abnormalities includes a discussion of cytogenetic abnormalities among spontaneously aborted previable fetuses, and a series of case reports of cytogenetic syndromes. The other sections cover skeletal dysplasias, biochemical and metabolic aspects of developmental pathology, syndromes and malformations complexes, and cardiac teratogenesis. Papers on short rib polydactyly syndromes, the pathology of the liver and kidney in Meckel's syndrome and a discussion of the causes and pathogenesis of cardiac malformations appealed to the reviewer.

This book achieves its aim as a remarkable tribute to a distinguished pathologist and paediatrician. It is not a book which most non-specialist readers will want to own, but they should browse through it to indulge their own interests.

P J Berry
CONSULTANT PAEDIATRIC PATHOLOGIST
Bristol Royal Hospital for Sick Children

Children with Asthma: A Manual for Parents. 2nd ed. By Thomas F Plaut. Pp 269: $11·95 paperback. Pedipress, 1988.

This book is written by a paediatrician who clearly knows a great deal about children, parents, and asthma. He believes that, with proper information and understanding, parents can undertake most of their children's care, reducing emergency visits and hospital admissions to an unavoidable minimum. Basic facts about asthma and its management are presented in a clear, positive manner and supplemented by parents' descriptions of their children's problems and how they coped with them.

The sections on the assessment of asthma by monitoring 'The Four Signs of Asthma Trouble' (wheezing, recession, prolonged expiration, and increased respiration rate), keeping records, and using a peak flow meter are excellent and could be read with benefit by many doctors. Clear instructions are given on the use of metered dose inhalers, spacer devices, and nebulisers, but the drugs recommended are sufficiently different to confuse British parents (for example, nebulised metaproterenol instead of salbutamol). Dry powder inhalers, so widely used in this country, are not mentioned. Prophylactic treatment is based on theophyllines, though sodium cromoglycate is also approved. Inhaled steroids rate only a brief paragraph and are not mentioned at all in the case reports.

I liked the advice on how to choose a doctor (minimum criteria: gives written instructions, teaches and monitors use of devices, measures peak flow at each visit), when to seek specialist advice, and how to deal with accident and emergency departments and hospital admission.

Parents who can select appropriate information would benefit from reading this book and it could be a valuable basis for discussion at local asthma society meetings.

E J Hiller
CONSULTANT PAEDIATRICIAN
City Hospital, Nottingham

Computing for Clinicians. By Tim Chard. Pp 136; paperback £18. Elmore-Chard, 1988. ISBN 0–9512981–0–0.

This is an excellent small book which goes where few have dared to go. The author has bravely attempted the equivalent of organising a barbecue for vegetarians in writing a book for the clinician, who has even at this late stage in the millenium, no prior knowledge of computing.

The book succeeds in covering the basics and gently takes the reader into more complex areas. Those who have a reasonable experience of computers in medicine will find this a valuable source of references and succinct explanations which they might quote. Those who dare to confront their technophobia and would like a concise guide to the potential of computers in medicine should find this book stimulating.

A wide variety of topics are covered:

medical administration, explanation of the computer as part of medical machines, advice on computer data collection, computer aided diagnosis, treatment, and teaching. I found the section on computer aided medical decision making very helpful as it explained some of these concepts so clearly that I was able to continue to understand it beyond the time of actually reading it. The author backs up his opinions and explanations with good references and provides other valuable information such as addresses of on line databases (such as Medline).

Another word to those who instinctively dislike computers: they are here to stay, they can work evil by tangling confused clinicians into time wasting tasks, and they may be used by those in power to spread illusory irrelevant information to hide vital problems. However, they are strengthening our vision in computed tomography, extending our memory in on line literature databases, and supporting our wisdom in decision making. They have no morality but we have the responsibility to remain vigilant by understanding their potential for doing both good and harm. This book, provided it is updated as time moves on, is a valuable weapon in this important role of the clinician.

G Clayden
CONSULTANT PAEDIATRICIAN
St Thomas's Hospital, London

The State of the World's Children 1988. Pp 86: £2·95 paperback. UNICEF, Oxford University Press, 1988. ISBN 0–19–261723–0.

The best thing about this book is its ability to inform the reader in under 100 pages what we (as paediatricians and as citizens) can do to make children healthier. For those who wish to read no further, the keys are

- Better information to parents and children about simple health technologies.
- Antipoverty measures (including fairer trade and aid policies).
- Common cause between health workers, educators, the media, and big business in putting children first.

The *State of the World's Children* is UNICEF's Annual Report on global child health, aimed at a lay readership. It is cheap and well presented with fine graphics. It emphasises achievements rather than dwelling on tragedies and sometimes the glowing reports are too good to be true. The book is a marvellous source of good examples and a reminder of our global responsibilities, as well as of what we have in common with many developing countries. The data that pack the last few pages are a source of chilling wonder; they encourage inter country comparisons, suspect though these may be. Contrast Costa Rica (gross national product $1300, under 5's mortality 23/1000 live births) with Saudi Arabia (gross national product $8850, under 5 mortality 105/1000 live births):

	% Rural population with access to drinking water	*% Adult literacy rate (male/female)*	*TV receivers per 1000 population*	*% Defen- expenditure**
Costa Rica	82	94/93	77	3·0
Saudi Arabia	68	35/12	269	36

*% Of central government expenditure.

Many examples are given that we can lea from. In Bangladesh, immunisation me sages appear on matchboxes and in Colomb on electricity bills. Again in Colombi high school pupils visit families at home discuss oral rehydration. In Nepal, com books and songs describe hygiene ar diarrhoeal disease. The report emphasis the power that knowledge conveys and critical of doctors for failing to inform th patients sufficiently.

This report should be at the elbow every paediatrician and their unit manage When will we have a 'State of Britain Children'? It might just embarrass us in action.

A J R Waterst
CONSULTANT PAEDIATRICI
Newcastle General Hospit
Newcastle upon Ty

NEW FROM OXFORD

CHILD HEALTH CARE

* * * * * *

British Paediatric Association Manual on Infections and Immunizations in Children

Edited by **Angus Nicoll and Peter Rudd**

The unsatisfactory uptake of immunization in the UK is a major reason for the continuing morbidity of childhood infectious disease. This handbook summarizes the important childhood infections and gives simple, practical advice on current immunization and treatment.

0 19 261785 0, 376 pp., illus., paperback, March 1989
£9.95

Child Health in a Changing Society

British Paediatric Association

Edited by **John O. Forfar**

Disease, diet, environment, and life-style in childhood can affect physical and mental health in adult as well as early life. In this BPA book, aimed at both professionals and lay readers, experts examine some of the medical and social problems.

'an outstanding and challenging book.' **The Lancet**
0 19 261687 0, 320 pp. illus., paperback, May 1988 £9.95

Asthma

The Facts
Second Edition

Donald J. Lane and Anthony Storr

For this second edition, the text has been updated throughout. The new understanding of the mechanism of asthma is presented, and important new innovations in treatment are included.

Facts
0 19 261692 7, 194 pp., illus., Oxford Paperbacks, 1987
£4.95

Parasitic Infections in Pregnancy and the Newborn

Edited by **Caroline L. MacLeod**

Parasitic infections occur frequently in tropical regions, but there is little help available for those who have to treat diseases that affect pregnant women or newborn children. This book provides a reference and practical resource text.

0 19 261653 6, 316 pp., illus., April 1988 £35.00

Paediatric Problems in General Practice

Second Edition

Michael Modell and Robert Boyd

This book aims to help the GP with the problems of dealing with children, covering both common and rarer life-threatening problems. The new edition has been extensively rewritten and expanded, with new coverage of teenage motherhood, sexual abuse, allergy in disease, and other topics.

Oxford General Practice Series No. 13
0 19 261736 2, 332 pp., illus., paperback, October 1988
£15.00

OXFORD UNIVERSITY PRESS

Taylor & Francis

Bronchopulmonary Dysplasia

Edited by **Eduardo Bancalari,** *University of Miami School of Medicine, Florida, USA* and **J. Thomas Stocker,** *Institute for Pediatric Medical Education, Bethesda, Maryland, USA*

A well-illustrated, thoroughly referenced volume covering this increasingly frequent disease in premature infants. This book includes current advances in pathogenesis, pathophysiology, and clinical management, and also presents the most detailed descriptions to date of the pathology of acute, reparative, and long-standing ('healed') phases of BPD.

Hemisphere 0 89116 681 5 Cloth
441pp 1988 £50.00

International Directory of Pediatric Pathologists

Edited by **Ronald Jaffe,** *Children's Hospital, Pittsburgh, PA 15213, USA*

A thorough survey of more than 2,000 practicing pediatric pathologists from around the world, compiled by the editors of the respected journal *Pediatric Pathology*. This Directory is the definitive reference for locating research collaborators and consultants in particular areas of pediatric pathology.

Hemisphere 0 89116 880 X Cloth
c325pp Autumn 1989 c£89.00

ORDER FORM

Name________________________

Address________________________

____

Signature____________ **Date**________

Please send me________________________

☐ **I enclose my personal cheque / money order**
☐ **Please send an invoice**
☐ **Please bill my Access/Mastercard/Eurocard/ Visa/AMEX**

Card No.________________________

Expiry date________________________

Taylor & Francis
Rankine Road, Basingstoke, Hants RG24 0PR,UK
Tel: (0256) 840366
242 Cherry Street, Philadelphia, PA 19106-1906, USA

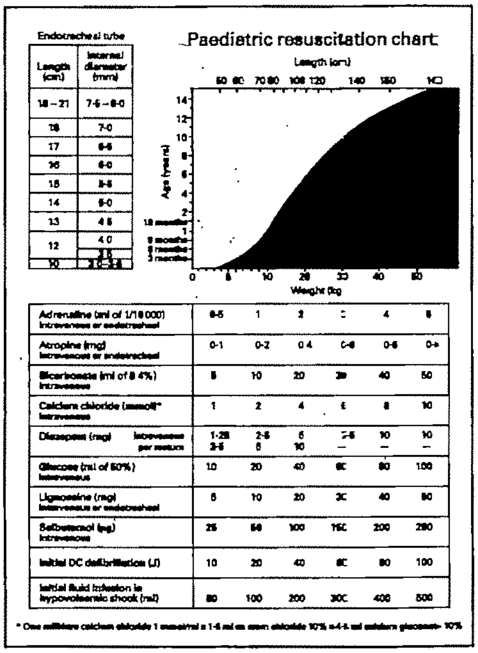
The Hospital for Sick Children in Toronto is looking to complement its professional staff and is seeking a

Paediatric Endocrinologist

This is a full-time faculty position that carries responsibility in the areas of clinical care, clinical research and teaching. Of additional interest, opportunities do exist in laboratory research.

Eligibility to work in Canada is essential. We invite qualified professionals to respond by submitting a curriculum vitae, **quoting reference # C158C**, to: Dr. Robert M. Ehrlich, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8.

HSC THE HOSPITAL FOR SICK CHILDREN



A child is dying: what do you do?

Resuscitating children is different from resuscitating adults—and more difficult. Because cardiorespiratory arrest in children is uncommon each doctor's experience of handling it is limited, and there is a tendency to forget the recommended drug doses; also, because children come in so many different sizes it is hard to judge the correct dose, especially if you do not know the child's weight. Yet delay or inaccuracy in treatment might be fatal. **The Paediatric Resuscitation Chart,** devised by Dr Peter Oakley and based on the guidelines of the Resuscitation Council (UK), gives you at a glance the essential information for making rapid and accurate decisions. The chart is available as an A2 size poster or a pocket sized postcard.

Poster: UK £3.50; Abroad £4.50; USA $9.00, including packing and postage, by air abroad.

Single copies of a postcard version of the chart are available, free of charge, on receipt of an A5 stamped addressed envelope (16cm x 24cm; 6in x 9in). Bulk orders please write to the Book Department.

Credit cards are accepted: ACCESS, VISA, AMERICAN EXPRESS (please give full details)

BMJ BRITISH MEDICAL JOURNAL, BMA HOUSE, TAVISTOCK SQUARE, LONDON WC1H 9JR

Archives of Disease in Childhood, 1989, **64,** 439–440

British Paediatric Association

Report from the British Paediatric Surveillance Unit

This third report on the activities of the British Paediatric Surveillance Unit (BPSU) presents the results of mailings between February and July 1988, and updates the results for July 1986 to January 1988 presented previously.[1]

Cases reported

The table shows, for each of the reportable conditions, the total number of reports received between July 1986 and July 1988 and the proportion of cases which on detailed follow up (as at 30 September 1988) satisfied the diagnostic criteria. Studies completed (X-linked anhidrotic ectodermal dysplasia, Lowe's syndrome, pilot study of childhood diabetes in the South Western region) and shown in previously published tables are not included.[1,2] The six new conditions not shown previously, studies of which began in 1988, are childhood onset diabetes mellitus, galactosaemia, drowning and near drowning, haemorrhagic disease of the newborn (all one or two year prospective studies) and rheumatic fever and congenital rubella syndrome/congenital rubella infection (both retrospective surveys included for one mailing only—January and April 1988 respectively). Respondents were asked to report all cases of rheumatic fever seen in 1987 and cases of congenital rubella born in 1986 and 1987.

The decision to include diabetes was a controversial one because it is not a rare disease, as is reflected in the large number of reports received. Kawasaki disease continues to be the next most frequently reported condition, although unlike observations in other countries no clear seasonal pattern is emerging. In contrast, reporting of haemolytic uraemic syndrome consistently increases in the late summer/early autumn. New reports of AIDS are continuing steadily.

Table *BPSU: reports received July 1986–July 1988*

Condition	*Total reports*	*Outcome of follow up by investigator*		
		Outcome known		*Not yet known‡*
		Report confirmed (% of known)*	*Report not confirmed†*	
AIDS in childhood	90	24 (33)	48§	18
Neonatal herpes	64	28 (57)	21	15
Reye's syndrome	105	43 (53)	38	24
Kawasaki disease	259	196 (86)	31	32
Haemolytic uraemic syndrome	141	92 (92)	8	41
Haemorrhagic shock encephalopathy syndrome	51	14 (67)	7	30
Subacute sclerosing panencephalitis	57	34 (81)	8	15
Galactosaemia‖	27	8 (40)	12	7
Drowning/near drowning‖	73	48 (96)	2	23
Childhood onset diabetes‖	647	416 (99)	5	226
Haemorrhagic disease of the newborn¶	19	1 (17)	5	13
Rheumatic fever**	15	—	—	—
Congenital rubella**	20	—	—	—

*Meets case criteria.
†Reporting error, duplicate or revised diagnosis.
‡Still being followed up by the investigator at 30 September 1988.
§Includes 23 cases who are HIV positive (14 symptomatic) but who do not meet the case definition for AIDS.
‖Study began in January 1988.
¶Study began in March 1988.
**Included for one month only (see text).

Participation

The average monthly response rate (proportion of cards returned 90 days after each mailing) was 89% (range 77% in South East Scotland to 100% in East Anglia) for the first quarter of 1988, compared with 90% for the previous quarter; 10 regions achieved 90% or more.

The BPSU continues to receive proposals for inclusion of new surveys. Notes to assist research workers in the preparation of a submission are available from the BPSU office. The Medical Coordinator can be consulted informally on proposed projects by telephone or letter.

Comment

Both the numbers of cases ascertained and the 'queue' of proposals for new surveys are measures of the usefulness of the BPSU as a research methodology. The two retrospective surveys mentioned above yielded information on cases either not previously ascertained through an existing, passive methodology (congenital rubella) or not readily available through routine national statistics (rheumatic fever).

Although more studies could clearly be accommodated if the number of reportable conditions were increased from the existing 12, a survey of respondents' views recently conducted through BPA Regional Representatives suggested (13 out of 16 replies received) that such an increase would be unwelcome. The BPSU Executive Committee (formerly the Scientific Advisory Committee) is seeking ways of resolving this dilemma.

Sir Peter Tizard retired from his position as Chairman of the BPSU Executive Committee in September 1988. Sir Peter's wisdom and experience have guided the development of the Unit from its earliest days to its current thriving position. He is succeeded by Professor J D Baum.

References

[1] Hall SM, Glickman M. The British Paediatric Surveillance Unit. *Arch Dis Child* 1988;**63**:344–6.

[2] Hall SM, Glickman M. Report from the British Paediatric Surveillance Unit. *Arch Dis Child* 1988;**63**:1117–8.

S M HALL
BPSU Medical Coordinator
and M GLICKMAN
BPSU Administrator

Archives of Disease in Childhood

You are invited to meet the editors on Tuesday 11 April 1989 at 9·15 pm at the Annual Meeting of the British Paediatric Association. The speakers will be Malcolm Chiswick on how papers are assessed and Bernard Valman on how the final decision is made.

Published by British Medical Association, Tavistock Square, London WC1H 9JR, and
printed in England by The Devonshire Press Ltd., Torquay

29.11.90

Vol 64 No 4 April 1989

ARCHIVES OF DISEASE IN CHILDHOOD

The Journal of the British Paediatric Association

Annotation

Living with a mentally handicapped brother or sister *Gath* 513

Original articles

Haemophilus influenzae type b disease in the Oxford region *Tudor-Williams, Frankland, Isaacs, et al* 517

Haemophilus influenzae type b conjugate vaccine trial in Oxford: implications for the United Kingdom *Tudor-Williams, Frankland, Isaacs, et al* 520

Chlamydia trachomatis infection in infants: a prospective study *Preece, Anderson, and Thompson* 525

Opsonic activity in serum from septic infants treated with intravenous immunoglobulin *Maródi, Kálmár, and Szabó* 530

Intradermal hepatitis B vaccine in thalassaemia and sickle cell disease *Mok, Underhill, Wonke, et al* 535

Newborn splenic volumes vary under different malaria endemic conditions *Corkill, Brabin, MacGregor, et al* 541

Measurement of nasal mucociliary clearance *Corbo, Foresi, Bonfitto, et al* 546

Management of oesophageal stenosis in epidermolysis bullosa dystrophica *Kern, Eisenberg, and Willis* 551

Minor congenital anomalies and ataxic cerebral palsy *Miller* 557

Prognostic value of creatine kinase BB-isoenzyme in high risk newborn infants *Ruth* 563

Cranial ultrasound assessment of gestational age in low birthweight infants *Murphy, Rennie, and Cooke* 569

Chronic renal failure and growth *Rees, Rigden, and Ward* 573

Neonatal urological ultrasound: diagnostic inaccuracies and pitfalls *Clarke, Gough, and Cohen* 578

Single dose trimethoprim for urinary tract infection *Nolan, Lubitz, and Oberklaid* 581

Growth hormone secretion in Turner's syndrome and influence of oxandrolone and ethinyl oestradiol *Massarano, Brook, Hindmarsh, et al* 587

Thyroid dysfunction after radiotherapy and chemotherapy of brain tumours *Livesey and Brook* 593

Sleeping body temperatures in 3–4 month old infants *Wailoo, Petersen, Whittaker, et al* 596

The thermal environment in which 3–4 month old infants sleep at home *Wailoo, Petersen, Whittaker, et al* 600

Skin colour and bilirubin in neonates *Knudsen and Brodersen* 605

Short reports

Low dose prednisolone in nephrotic syndrome *Choonara, Heney, and Meadow* 610

Does dexamethasone suppress the ACTH response in preterm babies? *Rennie, Baker, and Lucas* 612

Nephrocalcinosis in Shwachman's syndrome *D'Angio and Lloyd* 614

Successful treatment after 'drowning' in sand *Avital, Springer, Mogle, et al* 615

Ultraviolet irradiation for hepatic rickets *Kooh, Roberts, Fraser, et al* 617

Are babies more satisfied by casein based formulas? *Taitz and Scholey* 619

Personal practice

Management of diabetes mellitus *Johnston* 622

Neonatology—then and now *Walker* 629

Correspondence 630

Book reviews 640

National Health Service White Paper

Will it work for patients? *Appleyard* 643

BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

ISSN 0003-9888 ASTM CODEN: ADCHAK 64(4), 513–645, (1989)

Archives of Disease in Childhood

Editorial Committee

Editors: Bernard Valman and Malcolm Chiswick

Associate Editors: David Milner, Richard Robinson, Michael Silverman, and Brian Wharton

D P Addy
A G M Campbell
M J Dillon
I M Hann
M J R Healy
I A Hughes
D I Johnston
J W Keeling
J V Leonard
J K Lloyd
S P Lock
N McIntosh
P J Milla
E R Moxon
P O D Pharoah
L Polnay
N Richman
L Spitz
M J Tarlow
J F N Taylor
R M Winter

Technical Editor: Sue Heels

Editorial Assistant: Jacinta Marshall

Notes to Contributors
Papers for publication should be sent to the Editors, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR and should be prepared in accordance with the 'Instructions to authors' published in the January and June issues of the journal. Copies of these instructions may be obtained from the editorial office on receipt of a stamped addressed envelope.

Notice to Advertisers
Applications for advertising space and rates should be made to the Advertisement Manager, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR.

Notice to Subscribers
Archives of Disease in Childhood is published monthly. The annual subscription rates are £98 inland and £115 overseas (USA $165). Orders should be sent to the Subscription Manager, *Archives of Disease in Childhood*, BMA House, Tavistock Square, London WC1H 9JR. Orders can also be placed with any leading subscription agent or bookseller. (For the convenience of readers in the USA subscription orders, with or without payment, may also be sent to *British Medical Journal*, Box 560B, Kennebunkport, Maine 04046. All enquiries, however, must be addressed to the publisher in London.)

Subscribers may pay for their subscriptions by Access, Visa, or American Express by quoting on their order the credit or charge card preferred together with the appropriate personal account number and the expiry date of the card.

All enquiries regarding air mail rates and single copies already published should be addressed to the publisher in London.

COPYRIGHT © 1989 by *Archives of Disease in Childhood*. This publication is copyright under the Berne Convention and the International Copyright Convention. All rights reserved. Apart from any relaxations permitted under national copyright laws, no part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means without the prior permission of the copyright owners. Permission is not required to copy abstracts of papers or of articles on condition that a full reference to the source is shown. Multiple copying of the contents without permission is always illegal.

Second class postage paid, Rahway NJ. Postmaster: send address changes to: Archives of Disease in Childhood, c/o Mercury Airfreight International Ltd Inc, 2323 Randolph Avenue, Avenel, NJ 07001, USA.

Archives of Disease in Childhood, 1989, **64**, 513–516

Annotation

Living with a mentally handicapped brother or sister

For all children, home is the best place to be brought up. Plenty of evidence has accumulated that children's homes and other similar institutions, however well equipped and well trained the staff, are less good at fostering optimal development than the ordinary affectionate family. The child with a mental handicap is as susceptible to these family influences as the normal sibling. But does the presence of a child with a mental handicap, who needs more parental attention over a longer period, make that home a less good environment for the other potentially normal children? Should parents feel that they are being forced to sacrifice the well being of one child for the sake of another? Should parents who already have children of their own be allowed to adopt another with particular difficulties and more than the usual range of needs?

Families vary widely not only in their initial reaction to a distressing event but how they cope with the problems later. The notion that a family with a handicapped child must be a handicapped family is offensive to many and discredited from evidence of recent research. Emphasis now is put on the variety of strengths as well as the weaknesses of the people concerned.[1]

Sharing of family grief

No parent experiences the realisation that a child is handicapped—and hence unlikely to be able to fulfil even the most modest aims and ambitions that all parents have for their children—without suffering deep sadness and disappointment. Although everyone would like to spare children exposure to tragedy of any sort, the sharing of such an experience brings families close together and even though life is certainly changed, the cliché that it is not always for the worst is found to be true. The impact of mental handicap on the family will be different for the older children, who may have been able to appreciate the grief when the fact of handicap was established, either at the time of birth or later, than for children born subsequently who are less likely to be reported as having difficulties.

Parental problems

Unfortunately, the emotional trauma of having a child with a lasting handicap can be too much for some vulnerable personalities or fragile relationships. Early detrimental effects of the quality of the parents' relationship to each other have been noted within the first two years after the birth of a child with Down's syndrome. Children invariably do suffer when the relationship between their parents deteriorates to a situation of cold dislike or open hostility. Similarly, the sibling of the handicapped child is at risk when the initial grief felt by the parent has moved into a chronic depression. Sadly, these two problems often occur together as poor mental health in either parent is often found in conjunction with a bad marriage. Not only is the normal sibling more likely to show behavioural and emotional problems, but the mentally handicapped child is also similarly vulnerable and can show serious behaviour disorders, which can be particularly difficult to treat.[2]

Sharing of family burden

For most families, the rearing of a mentally handicapped child, even when adequately supported by medical services, with appropriate schooling and the opportunity of respite care, and with attendance or mobility allowances, necessitates much hard work relentlessly increasing as the child grows older and heavier. However, this load almost invariably falls on the mother.[3] Earlier work on siblings showed different effects on brothers and sisters,[4] and an explanation to account for the greater vulnerability of older sisters (particularly those from larger, relatively disadvantaged families) was that they were more involved in the practical problems of care. When specifically asked about what they did at home, however, children attending a group for siblings of children with a mental handicap denied being asked to do more chores than were their contemporaries in school.[5] The demands put upon the brothers and sisters was investigated in two more recent studies, and little evidence was found that they were being asked to carry a greater burden of household chores or minding a younger or more dependent sibling than a comparison group.[6 7] Older sisters were not the Cinderellas of community care any longer: that role was almost exclusively put upon the mother.

Severe behaviour problems, a common accompaniment of mental handicap in childhood, greatly increases the problems at home for the parents and often for the brothers and sisters as well.

Deprivation of parental attention

There might just not be enough of the mother's time or energy to go round. This situation can certainly happen and many families appreciate the chance to relax or have the sort of fun with their other children that is impossible in the company of the mentally retarded child. To be successful respite care needs to be seen as something positive. Linking with another family who can sometimes share the care of the more difficult member of the family, as would the ideal uncle or aunt, has been a very successful way of making respite care a positive experience all round.

Another possible myth is that parents commonly attempt to 'make up' to the handicapped child at the expense of their other normal children. Dividing attention equably among children of different ages with very different needs is a not uncommon problem of family life. No study has offered any objective evidence that parents of mentally handicapped children reserve significantly less time or attention for their normal children than do any other parents in what are regarded as normal families. On the contrary, many parents are very sensitive about the possibility of neglecting their other children. Most workers who study families in depth or over a long period are much impressed by the adaption and by the normality of those involved.[1]

Excessive expectations

It has also been suggested that parental ambition thwarted by the mental handicap of one child might be transferred in a detrimental way on to another child in the family. Most clinicians have seen such a situation arise but it is not common, certainly not inevitable nor even typical. Such increased expectations were seen in studies published 20 years ago when parents had little contact with the handicapped child and certainly no chance of feeling pride in any achievement. There are still families where the handicap of a child takes on an unusually great importance—for example, a handicapped first born son in many cultures.

Embarrassment and stigma

Attitudes towards mentally handicapped people, particularly children, have become much more positive over the past 20 years and this is mirrored in the studies of successive cohorts of families. It was not uncommon for the handicapped member of the family to have been admitted to long stay institutions and thereafter if not forgotten then never mentioned so that new members of the family might never know of the existence of such a person. When the secret has been revealed, as in the case of a family with a genetically determined disorder, the inquiries after the diagnosis have opened up deep rifts between members of the family. More open and accepting attitudes, which owe much to parent groups, mean that mentally handicapped children are now commonly seen with their families or schools enjoying ordinary activities in the community. Different cultures, however, within the United Kingdom, may still feel shamed by a handicapped child and fear returning to visit relatives in even countries in the European Community as well as developing countries because of ignorance, prejudice, and outright antagonism towards a handicapped child, which will extend also to a sibling.

Brothers and sisters reflect parental attitudes. It has been shown that when mothers and fathers were affectionate and actively encouraging their handicapped child then so were the siblings, who were also more often seen in a positive light by the parents.[8] In research studies of families, most of whom rarely visited hospitals or clinics, much robust determination to make the best out of their child and the situation they found themselves in created a strong sense of unity involving both parents and the other siblings. In hospitals, particularly centres to which families are referred away from their local services, the disillusioned families who still search for diagnoses or answers to apparently intractable problems are more common. In this situation, the brothers and sisters often identify with the disappointment and hostility expressed by the parents towards doctors and other services. It is the bias made by the referral that makes this sort of family seem so familiar.

Sociodemographic factors

As with other children, there are other environmental influences on the brothers and sisters in families. For example, there is some evidence suggesting that it is easier for children if there is more than one normal sibling, as deviancy is lowest in sibships of three or four.[4] Larger families are relatively common in families with a child with Down's syndrome in all social groups, but family size can not been seen as advantageous. Mental handicap in the family always brings hard work and has often crushed cherished hopes, but in conditions of social disadvantage, poorly paid unskilled work, unemployment, or bad housing it is particularly difficult for all children in the family. Some of the saddest families have been found among the ethnic minority groups as they had to contend with isolation and prejudice as well as the other social problems.

Achievement at school

Learning problems in brothers and sisters are more often found where no medical explanation could be given for the mental handicap itself.[7] Medical diagnoses, such as demonstrable brain damage, metabolic disorders, and chromosomal anomalies, are more often found in the more severely handicapped, while mental handicap in the mild range is more often associated with cultural disadvantage. The intellectual abilities of siblings of children with a severe handicap are greater than those of siblings of children with a mild mental handicap.[9] Brothers and sisters of children with Down's syndrome perform at school to a very similar standard to that of others in the same school class. When the siblings of children with no medical explanation for the handicap were compared with others in the same school class, there were significantly more among the sibling group with serious reading problems. In addition, such children were more often found in less advantaged areas where the others in the school had a higher rate of reading problems than did the sibling of a child with Down's syndrome or their control child in the same school class. Behaviour problems in the siblings were much more common in those who had significant problems with reading.

Do the brothers and sisters of handicapped children need help?

It is of course necessary that appropriate help be given to those children who are encountering major difficulties at school as a third of the siblings of children with no medical diagnosis were more than two years behind in reading. Similarly children in families who were being driven apart by marital disharmony or chronic mental illness in a parent may well require specific treatment for themselves as well as attention being paid to the underlying problem. But do these brothers and sisters need special help just because they are siblings of children with mental handicaps? Many object to the assumption that they do, just as they and their parents dislike being thought of as a handicapped family. As one remarked, 'I hate that word "sibling". It is as if there was something odd about me too'. Groups, not surprisingly, have not been conspicuously successful. Welcoming open days at the special schools showing how children with multiple disabilities can be taught, with demonstrations of the use of computers or instruction in a sign language such as Makaton, can be very helpful and much appreciated. It is no coincidence that many teachers, social workers, and nurses working in the field of mental handicap have a brother or sister with that disability.

Should specialist treatment for behaviour problems be offered to the retarded child and his family, getting to know the other children can be very helpful both in understanding the way the problem has arisen or been maintained and in continuing with treatment programmes. However, family treatment with a therapist who is ignorant about mental handicap can be a disaster. Treatment of all sorts must follow accurate assessment and the sharing as far as possible of knowledge about all the implications of the handicap.

What does seem to be helpful is to foster the self esteem of other children in the family by giving them the chance to shine, and it may be in a different direction. A counsel of perfection perhaps, but insistence on involvement in groups or family treatment can preclude that option. The other children do need information that can help them deal with ignorance or prejudice or can help them plan their own futures, particularly if the disorder concerned has a genetic basis.

Conclusion

There are many families who can prove that it is possible to be a loving and resourceful parent who can provide a stimulating and happy home to children of contrasting abilities and apparently conflicting needs. There is much to learn from such parents and their children that can help in understanding ordinary as well as extraordinary families. The provision of relevant services for children with disabilities including mental handicap and effective help for those who need it must follow an appreciative appraisal of families rather than a patronising assumption that all their individual quirks can be attributed to inevitable 'stress'.

References

[1] Byrne EA, Cunningham CC, Sloper P. *Families and their children with Down's syndrome: one feature in common.* London: Routledge, 1988.

[2] Gath A, Gumley D. Behaviour problems in retarded children with special reference to Down's syndrome. *Br J Psychiatry* 1986;**149**:156–61.

[3] Dupont A. A study concerning the time-related and other burdens when severely handicapped children are reared at home. In: Epidemiological Research as Basis for the Organisation of Extramural Psychiatry. *Acta Psychiatr Scand* 1980;**62** (Suppl 285):2249–57.

[4] Gath A. Sibling reactions to mental handicap: a comparison of the brothers and sisters of mongol children. *Child Psychol Psychiatry* 1974;**15**:187–98.

[5] Hart D, Walters J. *Brothers and sisters of mentally handicapped children.* London: Thomas Coram Research Unit, University of London; 1979. (Research report.)

[6] Lobato D, Barbour L, Hall LJ, Miller CT. Psychosocial characteristics of preschool siblings of handicapped and nonhandicapped children. *J Abnorm Child Psychol* 1987;**15**:329–38.

[7] Gath A, Gumley D. Retarded children and their siblings. *J Child Psychol Psychiatry* 1987;**28**:715–30.

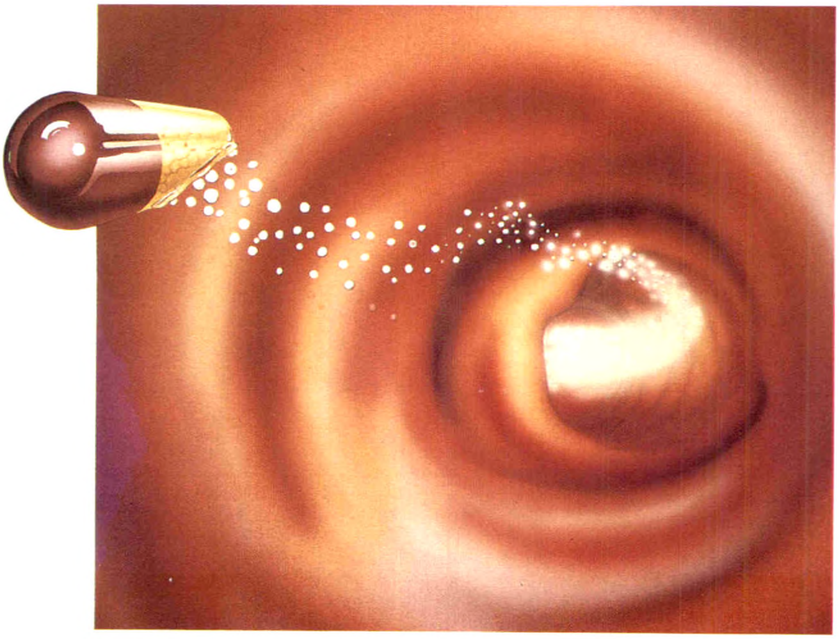
[8] McHale SM, Sloan J, Simeonsson RJ. Sibling relationships of children with autistic, mentally retarded and nonhandicapped brothers and sisters. *J Autism Dev Disord* 1986;**16**:399–413.

[9] Broman S, Nichols PL, Shaughnessy P, Kennedy W. *Retardation in young children. A developmental study of cognitive deficit.* New Jersey: Lawrence Erlbaum Associates, 1987.

A GATH
Hilda Lewis House,
Bethlem Royal Hospital,
579 Wickham Road, Shirley,
Croydon CR0 8DR

PROGRESS

In The Management Of Cystic Fibrosis



creon®

pancreatin

RIGHT ON TARGET – RIGHT FROM THE START

Prescribing Information – Presentation: Brown-yellow capsules containing enteric coated granules of pancreatin equivalent to: 9,000 BP units of amylase, 8,000 BP units of lipase, 210 BP units of protease. Available in packs of 100. Basic NHS price £13.33. **Indication:** Pancreatic exocrine insufficiency. **Dosage and administration:** Adults and children: Initially one or two capsules with meals, then adjust according to response. The capsules can be swallowed whole, or for ease of administration they may be opened and the granules taken with fluid or soft food, but without chewing. If the granules are mixed with food, it is important that they are taken immediately, otherwise dissolution of the enteric coating may result. **Contra-indications, Warnings, etc:** Contra-indications: Substitution with pancreatic enzymes is contra-indicated in the early stages of acute pancreatitis. Warnings: Use in pregnancy: There is inadequate evidence of safety in use during pregnancy. The product is of porcine origin. Rarely cases of hyper-uricosuria and hyper-uricaemia have been reported with high doses of pancreatin. Overdosage could precipitate meconium ileus equivalent. Perianal irritation could occur, and, rarely, inflammation when large doses are used. **Product Licence Number:** 5727/0001. **Name and address of Licence Holder:** Kali Chemie Pharma GmbH, Postfach 220, D-3000, Hannover 1, West Germany.

duphar Further information is available from:
Duphar Laboratories Limited, Gaters Hill, West End, Southampton SO3 3JD. Tel: 0703 472281.

CRAd/CF/1/89

HAMAD MEDICAL CORPORATION

1,200 bed referral facility, and is the main Health establishment in the country with its modernly equipped facilities, invites qualified applicants for

NEONATOLOGY POSITIONS AT ALL LEVELS.

Our Paediatric Department consists of:
52 Unit Neonatal Intensive Care Unit;
18 Ventilator Units; 34 Step Down and Isolation Units;
10,000 Deliveries in 1988.

REQUIREMENTS:
Completed Paediatric and Neonatology Training; Post Training experience required for higher levels.

BENEFITS:
Attractive tax free salaries based on qualification and experience; Free Furnished Accommodation; Round trip air ticket; 40–50 days annual paid leave; Contracts for 3 years renewable upon mutual agreement.

HOW TO APPLY:
Qualified applicants should send complete C.V. with contact telephone number to:

Attn.: MEDICAL DIRECTOR, Hamad Medical Corporation, P.O. Box 3050, Doha, State of Qatar, Arabian Gulf.

COURSE

CHILD ABUSE
& NEGLECT

PREPARATION FOR COURT

A 3 day course commencing
14–16 June 1989—
Postgraduate Centre,
Southmead Hospital, Bristol
covering:—

Problems Related to Child Abuse, Sexual Abuse, Communicating with Children, Collecting Forensic Evidence, Preparation of Court Reports, Court Proceedings & Pitfalls, After Cleveland.

For further details and application form please contact:—

Dr Jean Price, D.S.C.M.O.
Community Child Health Services,
Westgate House, Southmead Hospital,
Westbury-on-Trym, Bristol BS10 5NB.

14th Annual

FLORIDA SUNCOAST
PEDIATRIC
CONFERENCE

IMMUNOLOGY
IMMUNIZATIONS
DERMATOLOGY
AIDS

June 18–21, 1989
Tradewinds Resort Hotel
St. Petersburg Beach

UNIVERSITY OF
SOUTH FLORIDA
COLLEGE OF MEDICINE

ALL CHILDREN'S
HOSPITAL

For information-registration contact:
CAROLYN MOORE
(813) 892–4188

Archives of Disease in Childhood, 1989, **64,** 517–519

Original articles

Haemophilus influenzae type b disease in the Oxford region

G TUDOR-WILLIAMS,* J FRANKLAND,* D ISAACS,* R T MAYON-WHITE,†
J A MACFARLANE,‡ M P E SLACK,§ E ANDERSON,§ D G REES,‖ AND E R MOXON*

**University Department of Paediatrics, †Department of Community Medicine, Manor House, and ‡Department of Microbiology and Public Health Laboratory, John Radcliffe Hospital, Oxford; §Department of Community Health, Radcliffe Infirmary, Oxford; and ‖Department of Computing and Mathematical Science, Oxford Polytechnic*

SUMMARY A prospective survey of children in the Oxford region identified 200 cases of systemic *Haemophilus influenzae* type b disease in the first three and a half years of the study. The annual incidence in children less than 5 years of age was 33·4/100 000. This represents a cumulative incidence of one systemic infection in 600 children before their 5th birthday. The mortality was 5·0%. The risk of *H influenzae* type b meningitis was one in 850 with a mortality of 5·6%, and substantial morbidity among survivors.

From the total live birth rate, about 1300 cases of systemic *H influenzae* type b disease, over 900 cases of *H influenzae* type b meningitis, and 65 deaths would be predicted annually in children in the United Kingdom.

Haemophilus influenzae type b is a leading cause of bacterial meningitis in children in the United Kingdom.[1] It causes epiglottitis and less commonly may present as cellulitis, septic arthritis, pneumonia, empyema, or pericarditis.[2 3] Vaccines for *H influenzae* type b that are protective in infancy are now at an advanced stage of development.

No comprehensive data exist for the United Kingdom from which reliable estimates of incidence, mortality, and morbidity can be made for these diseases. A survey in an inner city area of Birmingham from 1973–84 estimated the incidence of severe *H influenzae* infection to be at least one in 950 children,[4] which is equivalent to an annual incidence of 21/100 000 children aged less than 5 years. Reports for 1984–7 to the Communicable Disease (Scotland) Unit indicate an annual incidence of systemic *H influenzae* type b disease of 28/100 000 children aged less than 5 years.[5] Laboratory data for Gwynedd, Wales from 1981–4 yield an annual incidence of 45·2/100 000 children aged less than 5 years.[6] These are higher than previous estimates from the United Kingdom[7 8] and approach the incidence figures for children aged less than 5 years from recent American series (Minnesota, 1982–4: 68/100 000/year[9] and Monro County, New York, 1982–3: 64/100 000/year[10]).

In order to provide accurate epidemiological information before the introduction of any intervention, a prospective survey was established in the Oxford region in 1985, and we report data from the first three and a half years.

Patients and methods

From 1 January 1985, any clinical isolates of *H influenzae* from normally sterile body fluids (for example, blood, cerebrospinal fluid, or joint aspirates) obtained from children under 10 years of age have been sent with brief clinical details from the microbiology laboratories throughout the Oxford region to the Public Health Laboratory Service Laboratory, John Radcliffe Hospital, Oxford. Serotyping, biotyping, and antibiotic sensitivity have been confirmed and thus only data on bacteriologically proved systemic *H influenzae* disease has been included. Isolates from children who have died outside hospital (for example, from unexpected infant deaths undergoing postmortem examination by the coroner) have been included. We have included all cases admitted within the region even if only temporarily resident, but have not included children from the region admitted elsewhere. The geographically defined denominator population was

2 438 000, of which 166 800 were children under 5 years of age according to data from the Office of Population Census and Survey for 1986. The study is still in progress and the data presented here include all cases up to 30 June 1988.

All 35 survivors of meningitis from the first year of surveillance were reviewed two years later by examination of their medical records and by contacting their general practitioners, health visitors, and community paediatricians. This additional study aimed to identify unequivocal serious morbidity among survivors.

The studies were approved by the Central Oxford Research Ethics Committee.

Results

A total of 219 cases of systemic disease caused by *H influenzae* were recorded in a three and a half year period in children less than 10 years old. 200 (91%) were due to serotype b organisms, the rest being due to non-typable (non-capsulated) strains. No other serotypes were implicated as systemic pathogens.

Of the *H influenzae* type b infections, 195 (97·5%) occurred in children under 5 years and 138 (69%) in children under 2 years of age. Only 20 (10%) occurred in children under 6 months, suggesting that this age group is relatively protected. The estimated annual incidence for systemic *H influenzae* type b disease was 33·4/100 000 children aged less than 5 years. The cumulative risk in this mixed rural and urban population for children by their 5th birthday was 1:600.

The clinical presentations of these 200 cases of *H influenzae* type b infection are summarised by age in the table. The annual incidence of *H influenzae* type b meningitis was 23·6/100 000 children aged less than 5 years, giving a cumulative risk of 1:850 children by their 5th birthday.

One child had sickle cell disease, and another had non-syndromic dysmorphic features, otherwise there were no recognised predisposing factors. No secondary cases involving siblings or close contacts were documented in this series.

Table *Clinical presentations by age of 200 cases of systemic H influenzae type b disease in children in the Oxford region January 1985–June 1988*

	Age (years, months)				*Total No (%)*
	<1·0	*1·0–1·11*	*2·0–4·11*	*>5·0*	
Meningitis	60	45	33	4	142 (71)
Epiglottitis	1	6	15	1	23 (12)
Cellulitis	11	0	1	0	12 (6)
Bone/joint infection	4	3	5	0	12 (6)
Pneumonia	3	1	2	0	6 (3)
Bacteraemia	3	1	1	0	5 (2)

Ampicillin resistance was found in 11·3% of *H influenzae* type b isolates: all the resistant strains produced β-lactamase. Of the non-typable isolates, 15·8% produced β-lactamase and one of these was also chloramphenicol resistant.

There were 10 recorded deaths, eight of which were due to meningitis, one due to epiglottitis, and one to bacteraemia. The age range of those who died was from 3 months to 5 years (median=1 year 2½ months). Five of these cases were diagnosed at postmortem examination after sudden unexpected deaths. The mortality rate for all systemic *H influenzae* type b disease was 5·0%. *H influenzae* type b meningitis carried a 5·6% mortality, while other clinical presentations combined had a mortality of 3·4%.

Of the 35 survivors of meningitis in 1985, three have bilateral sensorineural hearing loss requiring amplification and a fourth has global development delay with severe learning difficulties. Thus over 11% of survivors have major neurodevelopmental sequelae. Information regarding lesser disabilities was not sought.

Discussion

The epidemiological patterns we observed are in keeping with comparable data from the United Kingdom,[6 8] United States,[11 12] and Australia[13] except for a lower incidence of septic arthritis. If there is any bias in our figures it is likely to be in underdetection of the less common manifestations of systemic *H influenzae* type b disease as appropriate cultures may not have been sent. Prior antibiotic treatment may have resulted in some missed cases if all cultures were negative.

Our mortality rates concur with recently published series.[8 13–15] As a number of these deaths occur before arrival in hospital, therapeutic refinements for systemic *H influenzae* type b disease are unlikely to substantially reduce mortality.

We acknowledge the limitations of uncontrolled follow up data in the assessment of morbidity after *H influenzae* type b meningitis: well controlled long term studies are lacking in the United Kingdom. Studies from the United States report a wide range of significant sequelae in 8%[16] to 37%[17] of survivors, although a recent 10 to 12 year follow up in Pittsburgh showed comparable academic achievements with sibling controls, despite a 21% frequency of neurological sequelae.[18] Our findings of over 11% with significant sequelae tend to confirm that there is an accumulating register of children with impairments after *H influenzae* type b meningitis despite modern methods of management.

The total live birth rate in the United Kingdom is 790 000/annum with an upward trend predicted over the next decade. Extrapolating from our data to a population of 3·95 million children aged under 5 years about 1300 cases of systemic *H influenzae* type b disease, over 900 cases of *H influenzae* type b meningitis, and 65 deaths would be predicted annually in the United Kingdom.

The Communicable Disease Surveillance Centre (CDSC) at Colindale received reports of 787 cases of *H influenzae* type b meningitis or bacteraemia from participating laboratories in England and Wales for 1987. Not all microbiology departments send data to CDSC so this is acknowledged as incomplete surveillance. There were an additional 83 cases reported to the Communicable Diseases (Scotland) Unit. Other national data collection systems such as statutory notification and hospital activities analysis have even greater limitations.

There is an urgent need for prospective studies to be set up in other regions to assess accurately the incidence of systemic *H influenzae* type b disease. Such baseline data will be essential to determine the effect of intervention such as active immunisation with one of the conjugate *H influenzae* type b vaccines.

We thank the clinicians and microbiologists in the Oxford region who have supported this study and Gail Davies for typing the manuscript.

References

[1] Young SEJ. Haemophilus influenzae. *PHLS Microbiology Digest* 1987;**4:**68–9.

[2] Todd JK, Bruhn FW. Severe Haemophilus influenzae infections. *Am J Dis Child* 1975;**129:**607–11.

[3] Finch RG. Uncommon haemophilus infections. *Br Med J* 1984;**288:**941–2.

[4] Dyas A, George RH. Ten years' experience of Haemophilus influenzae infection at Birmingham Children's Hospital. *J Infect* 1986;**13:**179–85.

[5] Communicable Diseases (Scotland) Unit. Weekly returns provided by the Scottish Health Service Laboratories, Ruchill Hospital, Glasgow G20 9NN.

[6] Howard AJ. Systemic disease produced by Haemophilus influenzae. In: Cole PJ, ed. *The pathogenesis of Haemophilus influenzae*. London: MCI International, 1987:55–66.

[7] Goldacre MJ. Acute bacterial meningitis in childhood. *Lancet* 1976;**i:**28–31.

[8] Broughton SJ, Warren RE. A review of Haemophilus influenzae infections in Cambridge 1975–81. *J Infect* 1984;**9:**30–42.

[9] Murphy TV, Osterholm MT, Pierson LM, *et al.* Prospective surveillance of Haemophilus influenzae type b disease in Dallas County, Texas and in Minnesota. *Pediatrics* 1987;**79:**173–80.

[10] Redmond SR, Pichichero ME. Haemophilus influenzae type b disease. An epidemiologic study with special reference to day-care centers. *JAMA* 1984;**252:**2581–4.

[11] Dajani AS, Asmar BI, Thirumoorthi MC. Systemic Haemophilus influenzae disease: an overview. *J Pediatr* 1979;**94:**355–64.

[12] Broome CV. Epidemiology of Haemophilus influenzae type b infections in the United States. *Pediatr Infect Dis J* 1987;**6:** 779–82.

[13] Gilbert GI. Epidemiology and prevention of invasive Haemophilus influenzae type b infection. *Aust Paediatr J* 1987;**23:**323–7.

[14] Trollfors B, Claesson BA, Strangert K, Taranger J. Haemophilus influenzae meningitis in Sweden, 1981–83. *Arch Dis Child* 1987;**62:**1220–3.

[15] Davey PG, Cruickshank JK, McManus IC, *et al.* Bacterial meningitis—ten years experience. *J Hyg (Camb)* 1982;**88:** 383–401.

[16] Feigin RD, Stechenber BW, Chang MJ, *et al.* Prospective evaluation of treatment of *Haemophilus influenzae* meningitis. *J Pediatr* 1976;**88:**542–8.

[17] Sproles ET, Azerrad J, Williamson C, *et al.* Meningitis due to *Haemophilus influenzae*: long term sequelae. *J Pediatr* 1969;**75:** 782–8.

[18] Feldman HM, Michaels RH. Academic achievement in children ten to twelve years after Haemophilus influenzae meningitis. *Pediatrics* 1988;**81:**339–44.

Correspondence to Professor ER Moxon, University Department of Paediatrics, John Radcliffe Hospital, Headington, Oxford OX3 9DU.

Accepted 3 January 1989

Archives of Disease in Childhood, 1989, **64** 520–524

Haemophilus influenzae type b conjugate vaccine trial in Oxford: implications for the United Kingdom

G TUDOR-WILLIAMS,* J FRANKLAND,* D ISAACS,* R T MAYON-WHITE,†
J A MACFARLANE,‡ D G REES,§ AND E R MOXON*

**University Department of Paediatrics, †Department of Community Medicine, Manor House, ‡Department of Community Health, Radcliffe Infirmary, Oxford, and §Department of Computing and Mathematical Science, Oxford Polytechnic*

SUMMARY The safety and immunogenicity of a *Haemophilus influenzae* type b conjugate vaccine was investigated in 103 infants immunised at 3, 5, and 9 months of age; the infants also received diphtheria, pertussis, and tetanus and polio vaccines. Side effects were compared with 99 matched infants receiving diphtheria, pertussis, and tetanus and polio vaccines only. No serious side effects were observed and the incidence of minor side effects was no greater in the recipients of *H influenzae* type b conjugate vaccine. Two doses of the vaccine (standard and low) were compared: geometric mean titres of serum anticapsular antibody rose from 0·11 µg/ml before immunisation to 26·4 µg/ml after three immunisations with the standard dose and 14·6 µg/ml with the low dose. The geometric mean titre among 21 unimmunised infants at this age was 0·06 µg/ml. Both doses therefore generated antibody concentrations likely to be protective after three immunisations. There were no non-responders.

Incorporation of an *H influenzae* type b conjugate vaccine into the primary immunisation schedule has the potential for preventing over 1000 cases of systemic *H influenzae* type b disease and 50 deaths each year in the United Kingdom.

Haemophilus influenzae type b causes potentially fatal systemic disease such as meningitis and epiglottitis and other serious infections affecting soft tissues, joints, and lungs. Recent studies[1 2] suggest that the incidence of *H influenzae* type b disease in the United Kingdom is higher than previously reported.[3]

The polyribosyl-ribitol phosphate capsule, which is specific to serotype b *H influenzae* organisms, is a major virulence determinant.[4] Serum antibody to the capsule has been shown to be protective in infants.[5]

Immunocompetence to polysaccharides matures more slowly than to proteins and lipopolysaccharides. Active immunisation using purified polyribosyl-ribitol phosphate is ineffective in children less than 18 months of age[6]; they constitute a major proportion of the population at risk. A conjugate of a polysaccharide hapten and a carrier protein gives T cell dependent properties to the polysaccharide[7-9] with better immunogenicity in young children and predominantly IgG antibody responses that can be boosted.[10] Concentrations of antibody induced by immunisation can be higher than those after natural infection at the same age.[11] At least four different conjugates are undergoing clinical evaluation,[10 12-14] and one large efficacy study has been published.[14] It has been shown that a conjugate (HbO–C) of oligosaccharides derived from polyribosylribitol phosphate linked to a non-toxic mutant diphtheria toxin[10] is more immunogenic than the polyribosyl-ribitol phosphate-diphtheria toxoid conjugate used in the first efficacy trial (H Peltola, J Eskola, H Kayhty, PH Makela. Immunogenicity of *Haemophilus influenzae* oligosaccharide-protein conjugate vaccine (HbO–C) compared to polysaccharide-protein conjugate vaccine (PRP–D) in infancy. Personal communication, 1988). No conjugate has been tested in infants resident in the United Kingdom or according to the British schedule of primary immunisation at 3, 5, and 9 months of age and there is a need to define the optimal dose of polysaccharide.[15] Our study aimed to examine the serum antipolyribosyl-ribitol phosphate antibody state of unimmunised infants in the United Kingdom and to provide safety and immunogenicity data comparing standard and low dose regimes using the HbO–C *H influenzae* type b conjugate vaccine.

Patients and methods

Two hundred and thirty two mothers living in and around the city of Oxford, with full term healthy babies born consecutively during a two month period, were invited to participate in the study of the *H influenzae* type b conjugate vaccine. Of these, 103 mothers (including one with twins) agreed to take part; thus 104 infants were enrolled into the 'index' group. The infants were randomised using batched envelopes to receive a 0·5 ml dose containing 10 μg or 2 μg oligosaccharide (*H influenzae* type b HbO–C conjugate vaccine lot No A2K61/22 without adjuvant (Praxis Biologics); 0·9% sodium chloride was used as a diluent). *H influenzae* type b vaccine was given intramuscularly on the same occasion as diphtheria, pertussis, and tetanus vaccine but in a different site (opposing anterolateral thighs) at 3, 5, and 9 months of age. Parents were given a standard form and asked to record any local or systemic reactions over the next five days and measure daily axillary temperatures. The families were routinely visited the next day. Venepuncture for serology was performed before immunisation at each visit and at 10 months. All venepunctures and immunisations were performed in the child's home by one of us (GT–W) and only one attempt at venepuncture was made on any one visit.

Local reactions to *H influenzae* type b conjugate and diphtheria, pertussis, and tetanus vaccines could be compared for each index subject. To obtain comparative data for systemic reactions, 192 mothers from the same area giving birth to full term healthy infants in the month on either side of the recruiting period for the *H influenzae* type b conjugate vaccine were approached. Of these, 97 families including three with twins (100 infants) agreed to participate. This 'comparison' group received vaccine for diphtheria, pertussis, and tetanus (and oral polio) at home but were not given *H influenzae* type b conjugate vaccine or placebo. The child was visited the next day and the parents were requested to record reactions and measure temperatures as in the index group. The same batch of diphtheria, pertussis, and tetanus vaccine (A0726A, Wellcome) was used for both the index and comparison groups. Blood was taken from a random sample of 21 of these infants only once, at 10 months, to examine concentrations of antibody in United Kingdom children unimmunised with *H influenzae* type b conjugate vaccine.

One family from each group moved and were lost to follow up; therefore our results relate to 103 infants in the index group (52 received the 10 μg dose of vaccine) and 99 infants in the comparison group.

Serum samples were separated on the day of venepuncture and stored in 0·5 ml aliquots at −70°C. The Farr type radioantigen binding assay for total serum antipolyribosyl-ribitol phosphate antibody,[16 17] using the recommended criteria of the Office of Biologics Research and Review,[18] was performed in duplicate at three initial dilutions in both our own laboratories and those of Praxis Biologics. For neat sera with low concentrations of antibody, we interpreted the standard curves down to 0·05 μg/ml (7–8% binding in our assays). End point dilutions up to 1:1000 were performed to give estimates of high concentrations of antibody. Polyribosyl-ribitol phosphate intrinsically labelled with tritium radioantigen was supplied by Dr Porter Anderson, University of Rochester, USA, and Office of Biologics Research and Review lyophilised standard reference serum (70 μg/ml) was supplied by Dr Carl Frasch, Bureau of Biologics, Federal Drug Administration, Bethesda, USA.

The trial was approved by the Central Oxford Research Ethics Committee.

STATISTICAL METHODS

The proportion of children in the index and comparison groups were compared for all adverse reactions by χ^2 tests using Yates's correction (or by Fisher's exact test if expected values were <5). The proportion of unimmunised infants at 3 and 10 months of age whose antibody concentrations were above 0·05 μg/ml were compared by χ^2 test using Yates's correction. Mann-Whitney U tests were used to compare antibody responses to the two doses of *H influenzae* type b conjugate vaccine at a given age. For each dose Wilcoxon signed rank tests were used to assess the responses to first, second, and third immunisations.

Results

The vaccine was well tolerated and highly immunogenic. After three immunisations, the 10 μg doses resulted in a rise in geometric mean serum antipolyribosyl-ribitol phosphate antibody titre from 0·11 at 3 months to 26·4 μg/ml at 10 months of age. The 2 μg doses generated lower responses at 10 months ($p=0{\cdot}007$) although the geometric mean titre rose from 0·11 to 14·6 μg/ml, and at both doses all infants achieved greater than four fold increases in antibody titre and 98% achieved values above 1·0 μg/ml (figs 1 and 2).

The 10 μg dose resulted in significant increases in

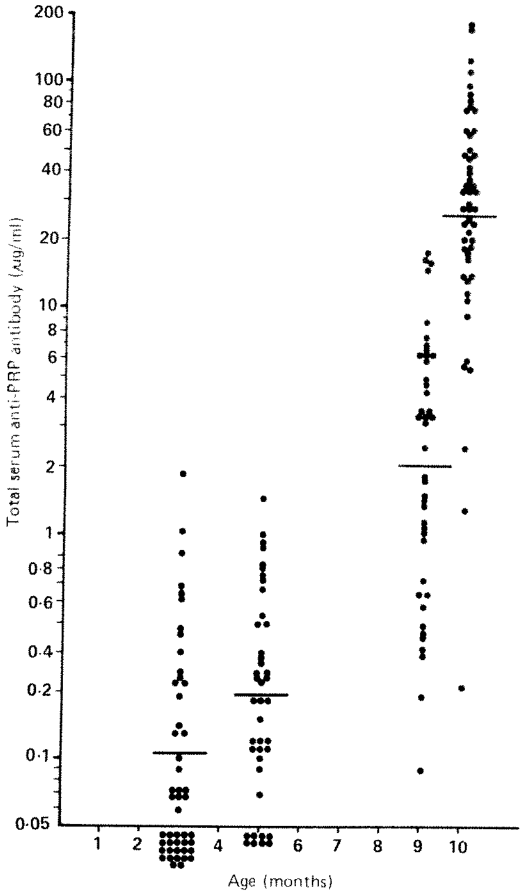


Fig 1 *Antipolyribosyl-ribitol phosphate (PRP) antibody concentrations in infants immunised at 3, 5, and 9 months with a 10 μg dose of H influenzae type b conjugate vaccine. Horizontal bars=geometric mean titres. (Results less than the lower limit of sensitivity of the assay were assigned a value of 0·05 μg/ml for calculation of the geometric mean titre.)*

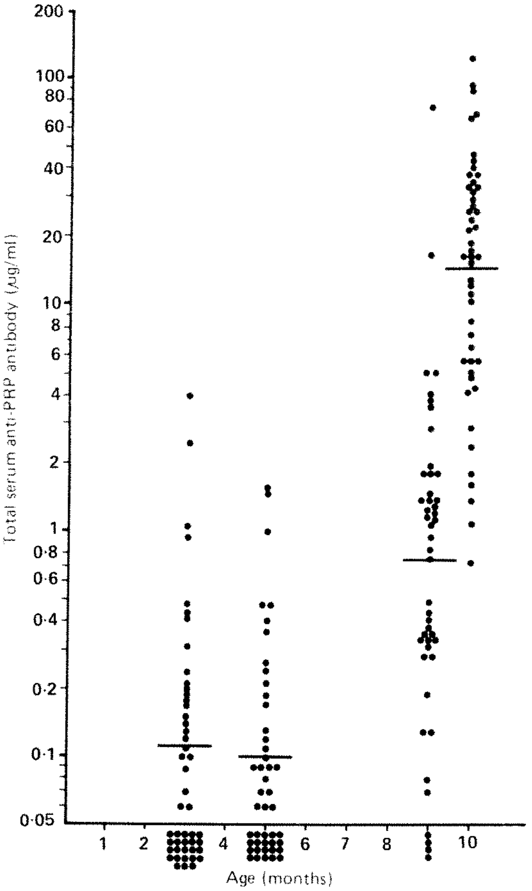


Fig 2 *Antipolyribosyl-ribitol phosphate (PRP) antibody concentrations in infants immunised at 3, 5, and 9 months with a 2 μg dose of H influenzae type b conjugate vaccine. Horizontal bars=geometric mean titres.*

antibody titre (p=0·0006) after one immunisation. No increase was observed after the first 2 μg dose (p=0·23). Geometric mean titres at age 5 months were 0·19 and 0·10 μg/ml respectively. After the second immunisation booster responses were noted with both dosage regimes: geometric mean titres at 9 months rose to 2·05 and 0·75 μg/ml respectively. The 2 μg dose produced a wider scatter of results, however, and four individuals had antibody concentrations below the limit of sensitivity of our assay.

In 21 infants from the comparison group who had not received the *H influenzae* type b conjugate vaccine, the geometric mean titre at 10 months was 0·06 μg/ml. There was a fall in antibody concentrations (p<0·01) when compared with the combined results for the index infants at 3 months of age in samples taken before their first immunisation with *H influenzae* type b conjugate vaccine (fig 3).

No major adverse reactions occurred in either group and no complications from venepuncture were observed. Adverse reactions did not differ significantly by dose of *H influenzae* type b conjugate vaccine and their results have been combined. A comparison of side effects is shown in the table. Local reactions defined as redness or swelling or warmth >2 cm occurred in 2% of index infants after administration of *H influenzae* type b conjugate vaccine and 19% after diphtheria, pertussis, and tetanus vaccine. Local reactions to diphtheria, pertussis, and tetanus vaccine in the comparison infants were of similar frequency. Systemic reactions

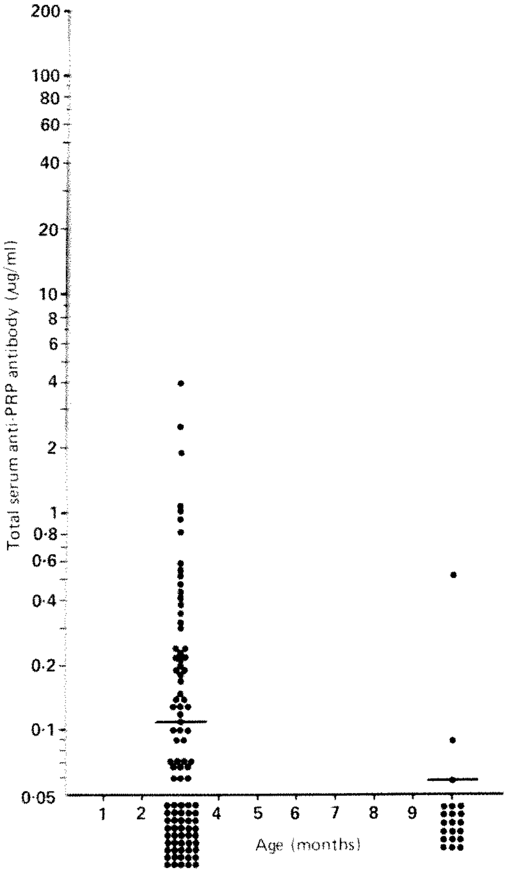


Fig 3 *Antipolyribosyl-ribitol phosphate (PRP) antibody concentrations in unimmunised infants in the United Kingdom. Horizontal bars=geometric mean titres.*

Table *Side effects of immunisation with H influenzae type b conjugate and diphtheria, pertussis, and tetanus vaccines compared with immunisation with diphtheria, pertussis, and tetanus alone*

	Index infants (n=103)	*Comparison infants (n=99)*
Local reactions (redness, swelling, or warmth >2 cm)		
Site of *H influenzae* type b conjugate:		
First immunisation	1	
Second immunisation	2	
Third immunisation	2	
Site of diphtheria, pertussis, and tetanus:		
First immunisation	24	21
Second immunisation	18	15
Third immunisation	18	21
Systemic reactions		
Axillary temperature >38°C		
First immunisation	5	7
Second immunisation	10	4
Third immunisation	9	19
Irritability >4 hours total		
First immunisation	25	27
Second immunisation	18	30*
Third immunisation	27	37
Persistent crying >1 hour		
First immunisation	25	41*
Second immunisation	11	26**
Third immunisation	11	19

*$p<0·05$; **$p<0·01$.

were similar or less frequent in the index children compared with those in the comparison group.

Discussion

The serum antibody concentrations observed in unimmunised infants at 3 months and 10 months are consistent with the decline in serum antibody observed in North American infants.[19] Both are consistent with the relative protection from *H influenzae* type b infection observed during the early months of life.

The *H influenzae* type b conjugate vaccine was well tolerated with a low frequency of local reactions and no increase in systemic side effects when given with diphtheria, pertussis, and tetanus vaccine as compared with infants receiving diphtheria, pertussis, and tetanus vaccine alone. It has been shown that another conjugate (polyribosyl-ribitol phosphate-D) can be mixed with diphtheria, pertussis, and tetanus vaccine and given as a single injection without adverse effects on safety or immunogenicity.[20]

The conventional dose of polysaccharide in polyribosyl-ribitol phosphate is 25 µg. A variety of doses from 10–25 µg have been employed in trials of *H influenzae* type b conjugate vaccines. We found that 2 µg of oligosaccharide in the *H influenzae* type b conjugate induces booster responses after a second immunisation at 5 months. The 2 µg dose, however, did not affect the decline in antibody concentrations after immunisation at 3 months, whereas a significant rise in antibody concentrations was observed after a 10 µg dose at this age. Given the pattern of susceptibility in young infants it is desirable to achieve immunological priming at as young an age as possible and our results suggest that a 10 µg oligosaccharide dose would be more appropriate than a 2 µg dose for the immunisation schedule in the United Kingdom.

There has been much debate as to what constitutes a 'protective' concentration of antibody[21]: titres >1·0 μg/ml are widely accepted as correlating with long term protection after immunisation with unconjugated polyribosyl-ribitol phosphate. The Finnish trial of polyribosyl-ribitol phosphate-D, however, disclosed a higher protective efficacy than would have been predicted from the immunogenicity data.[14] In view of the T cell dependent characteristics of responses to the conjugate vaccines it seems likely that the priming effect of one dose may be more important than achieving a designated post-immunisation antibody titre that correlates with protection but was based on experience with the unconjugated polysaccharide vaccine.

Our data and the results of studies of other candidate vaccines suggest that incorporation of immunisation for *H influenzae* type b into the schedule in the United Kingdom has the potential for preventing over 85% of systemic infection with *H influenzae* type b in children.[12-14] Extrapolating from the incidence of systemic *H influenzae* type b disease in the Oxford region, this would represent 1105 cases with their attendant long term sequelae and 55 deaths each year.

This and even higher estimates[1] of attack rates from other regions in this country make a compelling case for considering how active immunisation might be successfully implemented. The availability of safe, immunogenic, and protective conjugate vaccines strengthens the argument that wider intervention studies should proceed in the United Kingdom.

We thank all the families who took part in this study. We thank Dr WOC Cookson and Mrs Lin Barnetson for providing computing expertise and Miss Gail Davies for typing the manuscript. We thank Dr Porter Anderson for supplying the tritiated polyribosyl-ribitol phosphate and for his constructive criticism, and Praxis Biologics for materials.

References

[1] Howard AJ. Systemic disease produced by Haemophilus influenzae. In: Cole PJ, ed. *The pathogenesis of Haemophilus influenzae.* MCI International Ltd, 1987:55–66.

[2] Tudor-Williams G, Frankland J, Isaacs D, *et al.* Haemophilus influenzae type b disease in the Oxford region. *Arch Dis Child* 1989;**64**:517–9.

[3] Broughton SJ, Warren RE. A review of Haemophilus influenzae infections in Cambridge 1975–81. *J Infect* 1984;**9**:30–42.

[4] Moxon ER. The molecular basis of Haemophilus influenzae virulence. *J R Coll Physicians Lond* 1985;**19**:174–8.

[5] Santosham M, Reid R, Ambrosino DM, *et al.* Prevention of Haemophilus influenzae type b infections in high risk infants treated with bacterial polysaccharide immune globulin. *N Engl J Med* 1987;**317**:923–9.

[6] Peltola H, Kayhty H, Virtanen M, *et al.* Prevention of Haemophilus influenzae type b bacteremic infections with the capsular polysaccharide vaccine. *N Engl J Med* 1984;**310**: 1561–6.

[7] Avery OT, Goebel WF. Chemo-immunological studies on conjugated carbohydrate-proteins. II. Immunological specificity of synthetic sugar-protein antigens. *J Exp Med* 1929;**50**:533–50.

[8] Paul WE. *New approaches for inducing natural immunity to pyogenic organisms.* Washington DC: US Government Printing Office, 1973:157–66. (DHEW Publication No (NIH) 74–553.)

[9] Schneerson R, Barrera O, Sutton A, Robbins JB. Preparation, characterization and immunogenicity of Haemophilus influenzae type b polysaccharide-protein conjugates. *J Exp Med* 1980;**152**:361–76.

[10] Anderson P, Pichichero ME, Insel RA. Immunisation of 2-month-old infants with protein-coupled oligosaccharides derived from the capsule of Haemophilus influenzae type b. *J Pediatr* 1985;**107**:346–51.

[11] Kayhty H, Jousimies-Somer H, Peltola H, *et al.* Antibody response to capsular polysaccharides of group A and C Neisseria meningitidis and Haemophilus influenzae type b during bacteremic disease. *J Infect Dis* 1981;**143**:32–41.

[12] Claesson BA, Trollfors B, Lagergard T, *et al.* Clinical and immunologic responses to the capsular polysaccharide of Haemophilus influenzae type b alone or conjugated to tetanus toxoid in 18–23 month old children. *J Pediatr* 1988;**112**:695–702.

[13] Lenoir AA, Granoff PD, Granoff DM. Immunogenicity of Haemophilus influenzae type b polysaccharide—Neisseria meningitis outer membrane protein conjugate vaccine in 2- to 6-month old infants. *Pediatrics* 1987;**80**:283–7.

[14] Eskola J, Peltola H, Takala AK, *et al.* Efficacy of Haemophilus influenzae type b polysaccharide-diphtheria toxoid conjugate vaccine in infancy. *N Engl J Med* 1987;**317**:717–22.

[15] Black SB, Shinefield HR, Hialt RA, *et al.* Efficacy of Haemophilus influenzae type b capsular polysaccharide vaccine. *Pediatr Infect Dis* 1988;**7**:149–56.

[16] Farr RS. A quantitative immunochemical measure of the primary interaction between I*BSA and antibody. *J Infect Dis* 1958;**103**:239–62.

[17] Anderson P. Intrinsic tritium labeling of the capsular polysaccharide antigen of Haemophilus influenzae type b. *J Immunol* 1978;**120**:866–70.

[18] Frasch CE. Office of Biologics Research and Review. *Haemophilus influenzae type b radioimmunoassay, 4–6–87 revision.* Bethesda MD: Department of Health and Human Services, 1987.

[19] Granoff DM, Munson RS. Prospects for prevention of Haemophilus influenzae type b disease by immunisation. *J Infect Dis* 1986;**153**:448–61.

[20] Eskola J, Kayhty H, Gordon LK, *et al.* Simultaneous administration of Haemophilus influenzae type b capsular polysaccharide-diphtheria toxoid conjugate vaccine with routine DPT + inactivated poliovirus vaccination of childhood. *Pediatr Inf Dis* 1988;**7**:480–4.

[21] Kayhty H, Peltola H, Karanko V, Makela PH. The protective level of serum antibodies to the capsular polysaccharide of Haemophilus influenzae type b. *J Infect Dis* 1983;**147**:1100.

Correspondence to Professor ER Moxon, University Department of Paediatrics, John Radcliffe Hospital, Headington, Oxford OX3 9DU.

Accepted 3 January 1989

Archives of Disease in Childhood, 1989, **64,** 525–529

Chlamydia trachomatis infection in infants: a prospective study

P M PREECE,* J M ANDERSON,* AND R G THOMPSON†

**New Cross Hospital and †Public Health Laboratory Service, Wolverhampton*

SUMMARY In a prospective study of *Chlamydia trachomatis* infection in pregnancy, 198 mothers positive for chlamydial antigen were identified; the infants of 174 were followed for up to six months and *C trachomatis* was recovered in cell culture from 43 infants (25%). Conjuctivitis occurred in significantly more infants who were positive for *C trachomatis* (20 of 43, 47%) than in those who were negative (18 of 131, 14%). There were also significantly more lower respiratory tract infections among infants with positive cultures (six of 43, 14%, compared with three of 131, 2%). The chlamydial antigen enzyme linked immunosorbent assay (ELISA) was positive in 61 of 131 infants from whom *C trachomatis* was not recovered in cell culture. False positive results were usually associated with the isolation of *Staphylococcus aureus* from samples of pharyngeal aspirate.

Our results confirm that *C trachomatis* infection is a common cause of neonatal conjunctivitis, and respiratory infection in the first few months of life, with an incidence of 8·2/1000 live births. Because the infection is easily treated by oral erythromycin, however, screening during pregnancy is not warranted.

Chlamydia trachomatis infection is commonly transmitted from mother to infant in the perinatal period and is now recognised as the commonest cause of neonatal conjunctivitis.[1] It is also a significant cause of lower respiratory tract infection in infants 3–4 months old[2 3] and may be an important pathogen in otitis media.[4] Prospective studies in the United States have reported carriage rates in pregnancy of from 2 to 18%.[5-9] Transmission occurs in 28–61% of infants of mothers positive for *C trachomatis*. The incidence of *C trachomatis* infection in infants has not been documented in Britain, so the value of antenatal screening and treatment in reducing infant morbidity is not known.

We have previously reported the findings of a prospective study of *C trachomatis* infection in pregnancy in an obstetric population in a district general hospital and explored the maternal risk factors associated with infection and their association with perinatal morbidity and mortality.[10] In the present study we outline the natural history of *C trachomatis* infection in infants, the rate of transmission, complications of infection, and the persistence of carriage. Such data are necessary to assess the morbidity associated with *C trachomatis* in the infant population so that the benefits of an antenatal screening programme may be predicted.

Patients and methods

In a prospective study of *C trachomatis* infection in pregnancy, 3309 unselected women attending a district general hospital obstetric unit, between 1 September 1985 and 31 August 1986, were screened for *C trachomatis* infection on presentation in labour.[10] An endocervical swab was taken during routine vaginal and speculum examination using a cotton tipped plastic swab. Swabs were placed in transport media, stored at 4°C, and transported to the laboratory. Chlamydial antigen was detected using the Boots Celltech monoclonal antibody enzyme linked immunosorbant assay (ELISA).

As a result of this study 198 women positive for chlamydial antigen were identified. They were offered treatment for themselves and their partners, and invited to bring their infants to the paediatric clinic for follow up. Infants were seen at 3, 6, 12, and 26 weeks. They were examined for evidence of conjunctivitis, respiratory infection, and any other abnormality. At each visit pharyngeal aspirate and cotton tipped plastic swabs from the lower conjunctivae were collected and transported immediately to the laboratory, in chlamydia transport media.[11]

The samples were examined for the presence of chlamydial antigen by a monoclonal antibody

ELISA. Samples were also inoculated into cell culture medium containing Buffalo green monkey cells as previously described.[11] The diagnosis was based on the identification of characteristic intracellular inclusion bodies on Giemsa stained monolayers of cells. If all samples were negative on the ELISA on at least two consecutive occasions no further samples were collected and it was assumed that the organism had not been transmitted, though the infants were followed up to act as controls. If the presence of chlamydial antigen was confirmed by the detection of inclusion bodies in cell culture transmission of *C trachomatis* had occurred.

Infants with respiratory symptoms were investigated to exclude other causal organisms by routine microbiological and virus culture, and immunofluorescence for respiratory syncitial virus, of the nasopharyngeal aspirate. Infants with conjunctivitis were also investigated for other bacterial pathogens.

Infants treated with erythromycin or tetracycline by their general practitioners before investigation were excluded from the study. Symptomatic infants who were positive for *C trachomatis* were treated with tetracycline oily eye drops for conjunctivitis. Erythromycin (30 mg/kg/day) was added for those who did not respond to tetracycline alone, and was also used to treat infants with lower respiratory tract infections.

Results

During a one year period 198 mothers positive for chlamydial antigen were identified at risk of transmitting *C trachomatis* to their infants. Seven infants who had been treated with erythromycin or tetracycline before their first follow up visit were excluded, and 16 did not attend for follow up; the parents of one child refused to take part in the study. Infants of 174 mothers positive for chlamydial antigen were therefore followed up. Six further infants were excluded during the study because they were treated with either erythromycin or tetracycline in circumstances outside the protocol.

C trachomatis was cultured on at least one occasion from at least one site in 43 (25%) of the 174 infants (table 1), and was isolated from two infants who were delivered by elective caesarean section despite intact membranes. It was isolated from the nasopharyngeal aspirate alone in 21 infants, from conjunctival swabs alone in eight, and from both sites in 14.

C trachomatis was isolated from 32 of 174 infants (18%) at 3 weeks, decreasing to two of 92 infants (2%) at 26 weeks (figure). Infants who received antibiotics have been excluded from this figure. This suggests gradual loss of carriage in infants who acquired the organism but received no treatment. Of the 43 infants who acquired *C trachomatis* at any time in the study eight were positive for the first

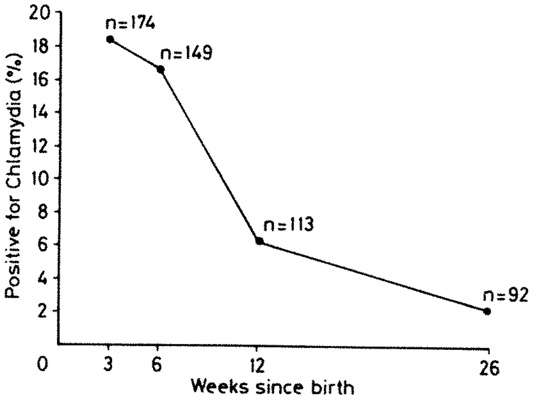


Figure *Prevalence of Chlamydia trachomatis infection in 174 infants exposed to maternal infection.*

Table 1 *Complications in 174 infants exposed to maternal Chlamydia trachomatis infection*

Complication	*No (%) of infants positive for chlamydia antigen*				*No (%) of infants negative for chlamydia antigen*
	Pharynx alone	*Eyes alone*	*Both*	*Total*	
None	16	0	3	19 (44)	109 (83)
Conjunctivitis alone	1	8	8	17 (40)	18 (14)
Conjunctivitis plus lower respiratory tract infection	0	0	3	3 (7)	0
Lower respiratory tract infection alone	3	0	0	3 (7)	3 (2)
Otitis media	1	0	0	1 (2)	1 (1)
Total	21	8	14	43 (100)	131 (100)

time at six weeks, two at 12 weeks, and one at 26 weeks. In the last three cases chlamydial antigen was detected at previous visits and only small numbers of organisms were recovered from cell culture.

NEONATAL CONJUNCTIVITIS

Conjunctivitis occurred in 20 (46·5%) of the 43 infants positive for *C trachomatis*, although the organism could not be cultured from conjunctival swabs in one (table 1). In eight cases the conjunctivitis was mild and resolved before the results of conjunctival swabs were available; it therefore required no treatment. In 12 cases it was sufficiently severe to require specific treatment; in five tetracycline eye drops alone, one erythromycin alone, and in six oral erythromycin was added because of failure of the tetracycline to clear the infection. The conjunctivitis resolved in all cases with or without treatment, and no long term effects were apparent at six months. Only one case presented before discharge from the maternity unit at one week, the remainder presenting at one to three weeks; the mean age at presentation was 14 days.

Bacterial conjunctivitis occurred in only 18 (14%) of 131 infants negative for *C trachomatis*, which is significantly less than among the infants who were positive ($p<0{\cdot}0005$). These cases were clinically less severe and responded promptly to local treatment with antibiotics. There were no cases of gonococcal conjunctivitis in either group.

RESPIRATORY TRACT INFECTIONS

Six infants positive for *C trachomatis* (14%) developed lower respiratory tract infections characterised by tachypnoea, hyperinflation, indrawing, and wheeze between 4 and 6 weeks. In each case *C trachomatis* was grown from phanygeal aspirates at the time of the illness. Three had previously had conjunctivitis; one had been treated with local tetracycline and in the other two the conjunctivitis had resolved without treatment. In one, respiratory syncytial virus shown by immunofluorescence in addition to the *C trachomatis*. All suffered mild respiratory symptoms, but only one infant required admission to hospital and radiographic changes were minor, consisting only of hyperinflation.

Three infants negative for *C trachomatis* (2%) had lower respiratory tract infections during the study ($p<0{\cdot}005$); no organisms were isolated in this group. *C trachomatis* associated respiratory tract infections resolved promptly in all infants, in two spontaneously and in four after oral treatment with erythromycin. Two infants (one from each group) suffered recurrent purulent otitis media with perforation. In one infant *Haemophilus influenzae* was isolated from the ear swabs and *C trachomatis* from pharyngeal aspirate but not from ear swabs. Treatment with amoxycillin was unsuccessful but she responded to erythromycin.

USE OF THE ELISA IN CHILDREN

The ELISA test was positive in 61 of the 131 infants in whom *C trachomatis* was not subsequently isolated in cell culture; in 53 of these *S aureus* was also isolated. In one infant a false positive ELISA was associated with the isolation of *Candida albicans*. False positive results were therefore common, particularly in pharyngeal aspirates. The results of this test alone were not sufficient to support the diagnosis of *C trachomatis* infection.

Discussion

The present prospective study has shown that infection with *C trachomatis* is transmitted to the neonate in a quarter of pregnancies complicated by this organism. In two cases this occurred despite intact membranes, confirming that this is not an unusual occurrence.[12] This rate of transmission gives rise to an estimate of neonatal infection of 14·7/1000 in our population (table 2). Symptomatic infection occurred in 24 of 43 (56%) infants, which represents an incidence of 8·2/1000. These figures are underestimates, as some of the 24 infants excluded (seven because of undocumented treatment by general practitioners) probably had symptomatic *C trachomatis* infection.

C trachomatis was recovered by cell culture in most infants in the first six weeks of life. The number of positive cultures declined with time, suggesting a gradual loss of chlamydial carriage as a commensal organism, in a similar manner to other perinatally acquired organisms such as *Mycoplasma hominis* or *Ureaplasma urealyticum*.[13] Interestingly,

Table 2 *Prevalence of maternal and neonatal Chlamydia trachomatis infection*

		Prevalence/ 1000 live births
No of mothers screened	3309	
No of mothers with chlamydia infection	198	60
No of infants followed up	174	
No of infants positive for chlamydia	43	14·7
No of infants with conjunctivitis	20	6·8
No of infants with lower respiratory tract infections	6	2·1
No of infants with otitis media	1	0·3
No of infants with sympatomatic chlamydial infection	24	8·2
No of infants with asymptomatic chlamydial infection	19	6·5

in three infants the cell culture was not positive until at least 12 weeks. Presumably only small numbers of organism were acquired at birth and time was required for the organism to replicate sufficiently to yield a positive result in cell culture. Postnatal acquisition, however, cannot be excluded.

C trachomatis is now the commonest cause of neonatal conjunctivitis.[1,14] The incidence in this study is higher than that previously reported,[15,16] but this could be due either to a different study design or to a real increase in the prevalence of maternal carriage of the organism.

Presentation before the second week of life is rare, so most children are initially treated by their general practitioners. If the condition is recognised promptly and treated appropriately, response is complete and late complications are rare. Oral erythromycin is now the treatment of choice for *C trachomatis* conjunctivitis because it is excreted in tears.[17] It also eradicates nasopharyngeal carriage so preventing the respiratory complications that occurred in three of our cases. Ocular prophylaxis with local erythromycin has been attempted in some units in the United States but it is not completely effective in preventing conjunctivitis and in no way alters the incidence of *C trachomatis* infection in the respiratory tract.[18]

Respiratory infections in the first four months are frequently caused by *C trachomatis*.[3] The rate in this study is an underestimate as seven children with conjunctivitis were treated with systemic antibiotics and so were no longer susceptible to *C trachomatis* respiratory infection, so the true rate was six of 36 (17%). As these seven children suffered the most severe conjunctivitis, the rate in untreated infants may even be higher. The clinical pattern may be indistinguishable from infection with respiratory syncytial virus except that there is no seasonal variation in incidence. Mixed infections may also occur so other respiratory pathogens (including other perinatally acquired organisms such as cytomegalovirus) should be sought.[3,13]

We found the ELISA a highly efficient method of screening women for chlamydial infection. It was also specific in infants with conjunctivitis, and false positive reactions were rare.[1] We do not at present recommend the test for the routine investigation of children with respiratory symptoms, as false positive reactions occurred frequently in pharyngeal aspirates (usually due to cross reactivity with *S aureus*).[19] Cell culture remains the most reliable method of diagnosis for samples of respiratory secretions though the specificity of the ELISA may be improved in the future (RG Thompson, personal communication). Direct immunofluorescence using monoclonal antibodies may also be used for the diagnosis of *C trachomatis* infection.[1] We did not use this method as we wished to assess a method that avoided both cell culture and microscopy compared with the standard method.

Screening in pregnancy to identify mothers at risk of transmitting *C trachomatis* to their offspring has been successfully carried out, and treatment in late pregnancy significantly reduces the risk of neonatal transmission.[20–22] We have doubts, however, about the cost effectiveness of screening as maternal chlamydial infection has no effect on perinatal mortality,[10] only 14% of infants of infected mothers suffered symptomatic infections, gradual loss of asymptomatic carriage occurs spontaneously, and treatment of symptomatic infants is safe and effective. Paediatricians and general practitioners must, however, have a high index of suspicion of chlamydial infection in infants as it is now the commonest cause of neonatal conjunctivitis and an important cause of respiratory infection during the first four months of life.

We thank our research assistant, June Sperring, the nurses of the childrens' day unit, and the staff of the microbiology department. Advice on computer analysis was given by Robert Lancashire of the department of social medicine, University of Birmingham, and the study was funded by the Wolverhampton Perinatal Research Fund and Abbott Laboratories.

References

[1] Rapoza PA, Quinn TC, Kiessling R, Green R, Taylor H. Assessment of neonatal conjunctivitis with a direct immunofluorescent monoclonal antibody stain for chlamydia. *JAMA* 1986;**255**:3369–73.

[2] Beam MO, Saxon EM. Respiratory tract colonisation and a distinctive syndrome in infants with C trachomatis. *N Engl J Med* 1977;**296**:306–10.

[3] Paisley JW, Laver BA, McIntosh K, Glode MP, Schachter J, Rumach C. Pathogens associated with acute lower respiratory tract infection in young children. *Pediatr Infect Dis* 1984;**3**: 15–9.

[4] Banks JR, Vanderdriesen G, Stark E. Chlamydia trachomatis in smears from eyes, ears and throats of children with chronic otitis media. *Lancet* 1985;**ii**:278.

[5] Frommell GT, Rothenberg R, Warg S, McIntosh K. Chlamydial infection of mothers and their infants. *J Pediatr* 1979;**95**:28–32.

[6] Hammerschlag MR, Anderka M, Semine DZ, McComb D, McCormack W. Prospective study of maternal and infantile infection with Chlamydia trachomatis. *Pediatrics* 1979;**64**:142–8.

[7] Heggie AD, Lumicas GG, Stuart LA, Gyveo MT. Chlamydia trachomatis infections in mothers and infants. *Am J Dis Child* 1981;**135**:507.

[8] Grossman M, Schachter J, Sweet R, Bishop E, Jordan C. Prospective studies in Chlamydia in newborns. In: Mardh PA, Holmes KK, Oriel JD, eds. *Chlamydial infections*. Amsterdam: Elsevier, 1982:213–6.

[9] Schachter J, Grossman M, Sweet RL, Holt J, Jordan C, Bishop E. Prospective study of perinatal transmission of C. trachomatis. *JAMA* 1986;**255**:3374–7.

[10] Preece PM, Ades A, Thompson RG, Brooks JH. Chlamydia trachomatis infection in late pregnancy: a prospective study. *Paediatric and Perinatal Epidemiology* 1989 (in press).

[11] Willis PJ, Johnson L, Thompson RG. Isolation of Chlamydia

using McCoy and Buffalo green monkey cells. *J Clin Pathol* 1984;**37:**120–1.

[12] Givner LB, Rennels MB, Woodward C, Huang S. Chlamydia trachomatis infection in an infant delivered by caesarean section. *Pediatrics* 1981;**68:**420–1.

[13] Stagno S, Brasfield DM, Brown MB, *et al.* Infant pneumonitis associated with cytomegalovirus, chlamydia, pneumocystis and ureaplasma: a prospective study. *Pediatrics* 1981;**68:**322–9.

[14] Winceslaus J, Goh BT, Dunlop EMC, *et al.* Diagnosis of ophthalmia neonatorum. *Br Med J* 1987;**295:**1377–9.

[15] Prentice MJ, Hutchinson GR, Taylor-Robinson D. A microbiological study of neonatal conjunctive and conjunctivitis. *Br J Ophthalmol* 1977;**61:**601–7.

[16] Pierce JM, Ward ME, Seal DV. Ophthalmia neonatorum in the 1980s: incidence, aetiology and treatment. *Br J Ophthalmol* 1982;**66:**728–31.

[17] Rettig PJ. Chlamydial infections in pediatrics: diagnostic and therapeutic considerations. *Pediatr Infect Dis* 1986;**5:**158–62.

[18] Hammerschlag MR, Chandler JW, Alexander ER, *et al.* Erythromycin ointment for occular prophylaxis of neonatal chlamydial infection. *JAMA* 1980;**244:**2291–3.

[19] Krech T, Gerhard-Fsadni D, Hoffman N, Miller SM. Interference of Staphylococcus aureus in the detection of Chlamydia trachomatis by monoclonal antibodies. *Lancet* 1985;**i:**1161–2.

[20] Podgare JK, Betts R, Alden E, Alexander ER. Effectiveness of maternal third trimester erythromycin in prevention of infant C. trachomatis infection. *Proceedings of the 20th Interscience Conference in Antimicrobial Agents and Chemotherapy.* New Orleans: American Society of Microbiology 1980:524.

[21] Schachter J, Sweet RL, Grossman M, Landers D, Robbie M, Bishop E. Experience with routine use of erythromycin for Chlamydia infection in pregnancy. *N Engl J Med* 1986;**314:**276–9.

[22] McMillan JA, Wiener LB, Lamberson HV, *et al.* Efficacy of maternal screening and therapy in the prevention of Chlamydial infection of the newborn. *Infection* 1985;**13:**263–6.

Correspondence to Dr PM Preece, The Children's Hospital, Ladywood Middleway, Birmingham B16 8ET.

Accepted 18 November 1988

Archives of Disease in Childhood, 1989, **64,** 530–534

Opsonic activity in serum from septic infants treated with intravenous immunoglobulin

L MARÓDI, Á KALMÁR, AND I SZABÓ

Department of Paediatrics, University Medical School of Debrecen, Hungary

SUMMARY Thirteen infants with staphylococcal sepsis and reduced opsonic activity received infusions of acid treated immunoglobulin together with antibiotics. Opsonic activity (using *Staphylococcus aureus* (type 42D) as the test organism), haemolytic activity of complement, and concentrations of complement C3 and IgG were measured in serum prepared before and after three days of treatment with immunoglobulin at a dose of 250–300 mg/kg/day. There was increased ingestion of *S aureus* by normal human granulocytes in the presence of fresh serum prepared after infusion of immunoglobulin and significantly increased opsonic activity of heat inactivated serum after treatment with immunoglobulin. The haemolytic activity of complement and concentrations of complement C3 were not influenced, and serum concentrations of IgG increased as the result of receiving a total of 800–900 mg/kg immunoglobulin over a period of three days. This study shows that administration of acid treated IgG to septic infants leads to functionally increased opsonisation.

Intravenous immunoglobulin is the treatment of choice for agammaglobulinaemia or hypogammaglobulinaemia. In patients with normal concentrations of gammaglobulin, immunoglobulins exert an immunomodulatory function.[1,2] High doses of immunoglobulins produce rapid increases in the platelet counts in patients with idiopathic thrombocytopenic purpura.[1,3] Intravenous immunoglobulins alone or with antiviral drugs may improve the efficacy of treatment of life threatening viral diseases, apparently by replacement of selectively missing or exhausted antibodies.[2] The combined use of intravenous immunoglobulins and antibiotics is effective in the treatment of neonatal sepsis, particularly in premature infants.[4,5]

Intravenous immunoglobulins contribute to antibacterial host defense by opsonising micro-organisms. Binding of specific antibodies of the IgG class, with or without subsequent binding of complement to the surface of bacteria, facilitates phagocytosis by granulocytes or mononuclear phagocytes.[6–8] In vitro studies have shown that intravenous immunoglobulin preparations that contain intact 7S IgG could mediate reasonable opsonic activity towards a number of bacterial pathogens and could enhance phagocytosis of these micro-organisms by granulocytes.[9] Addition of such a preparation to serum from neonates resulted in increased phagocytosis of group B streptococcus type III in the presence of adult granulocytes.[10]

In this study we report increased opsonisation using *S aureus* as the test organism in young infants receiving intravenous immunoglobulin for the treatment of established staphylococcal infection.

Patients and methods

Selected clinical and laboratory data of the 13 infants studied are shown in table 1. All these infants had septicaemia or other severe bacterial infections (meningitis, ventriculitis, pneumonia) caused by *S aureus* either singly or in combination with another bacterial pathogen. Congenital malformations in cases 4, 8, 9, and 12 could have been predisposing factors for the development of the severe infection. Case 13 developed a paraoesophageal abscess after swallowing a drawing pin that stuck in the oesophagus. When these patients presented with severe symptoms or septicaemia, or both, informed consent was obtained from the parents and conventional treatment with antibiotics was supplemented with intravenous immunoglobulin 250–300 mg/kg/day for three consecutive days. When immunoglobulin treatment was started, all the patients had already been receiving antibiotics for more than two days. During the immunoglobulin

Table 1 *Details of patients treated with immunoglobulin*

Case No	*Birth weight (g)*	*Gestational age (weeks)*	*Age of patient*	*Sex*	*Clinical diagnosis*	*Polymorphonuclear leucocytes* $(\times 10^9/l)$	*Source of bacteria*	*Bacteria cultured*
1	3500	41	2 Days	Female	Meconium aspiration, septicaemia	4·0	Blood	*S aureus, Klebsiella* species
2	3300	37	3 Days	Female	Septicaemia	10·0	Blood	*S aureus*
3	2800	35	5 Days	Male	Intracranial haemorrhage, septicaemia	6·0	Blood	*S aureus, Klebsiella* species
4	3000	37	7 Days	Female	Meningocele, meningitis	7·6	Cerebrospinal fluid	*S aureus*
5	3600	38	9 Days	Male	Umbilical sepsis, septicaemia	10·5	Blood	*S aureus*
6	3450	38	3 Weeks	Female	Pneumonia, septicaemia	9·8	Blood	*S aureus*
7	2500	33	4 Weeks	Male	Pneumonia	10·4	Pus	*S aureus*
8	3900	40	6 Weeks	Male	Hypoplastic lungs, pneumonia	4·6	Pus	*S aureus, Pseudomonas aeruginosa*
9	3200	40	8 Weeks	Female	Hypoplastic cricoid, septicaemia	14·0	Blood	*S aureus*
10	2450	40	8 Weeks	Female	Ventriculitis, septicaemia	8·0	Blood, cerebrospinal fluid	*S aureus, Pseudomonas aeruginosa*
11	3200	37	6 Months	Female	Mastoiditis, septicaemia	14·6	Blood	*S aureus*
12	3400	39	8 Months	Male	Hydrocephalus, shunt, septicaemia	12·6	Blood, cerebrospinal fluid	*S aureus*
13	2150	35	9 Months	Female	Paraoesophageal abscess, septicaemia	13·8	Blood, pus	*S aureus*

Table 2 *Details of control patients*

Case No	*Birth weight (g)*	*Gestational age (weeks)*	*Age of patient*	*Sex*	*Clinical diagnosis*	*Polymorphonuclear leucocytes* $(\times 10^9/l)$	*Source of bacteria*	*Bacteria cultured*
1	2800	36	2 Days	Female	Infantile respiratory distress syndrome, pneumonia, septicaemia	11·0	Blood	*S aureus, Escherichia coli*
2	2650	36	2 Days	Female	Oesophageal atresia, pneumonia	10·4	Pus	*S aureus*
3	2100	33	3 Days	Female	Meconium aspiration, respiratory distress syndrome, septicaemia	11·5	Blood	*S aureus, Klebsiella* species
4	2100	34	5 Days	Male	Aspiration pneumonia, septicaemia	9·4	Blood	*S aureus, Pseudomonas aeruginosa*
5	2700	40	6 Days	Female	Thrombophlebitis, septicaemia	6·1	Blood	*S aureus, Klebsiella species*
6	2200	31	3 Weeks	Female	Umbilical sepsis, septicaemia	8·2	Blood	*S aureus, Staphylococcus epidermidis*
7	3000	38	5 Weeks	Male	Pneumonia, diffuse intravascular coagulation	7·0	Pus	*S aureus*
8	2900	38	10 Weeks	Male	Otitis medis, septicaemia	3·1	Blood	*S aureus, Pseudomonas aeruginosa*
9	3200	37	5 Months	Female	Pneumonia, septicaemia	6·2	Blood	*S aureus*
10	3100	40	5 Months	Male	Retropharyngeal abscess	13·6	Pus	*S aureus*
11	2100	34	9 Months	Female	Osteomyelitis of tibia, septicaemia	17·2	Blood	*S aureus*
12	3550	40	10 Months	Female	Osteomyelitis of humerus	13·4	Pus	*S aureus*
13	3000	40	12 Months	Female	Pneumonia	7·6	Pus	*S aureus*

treatment none of the patients received blood or other blood products.

Table 2 shows the clinical and laboratory data of 13 infants who were reviewed retrospectively and acted as a historical control group. The criteria for selecting a patient as a control were one or more cultures of *S aureus* from blood or pus together with documented signs and symptoms consistent with septicaemia or other severe bacterial infection. Five patients were less than 2 weeks old, and the rest between 3 weeks and 12 months. There were seven patients with septicaemia, three with pneumonia, two with osteomyelitis (one with septicaemia), and one with a retropharyngeal abscess.

Blood samples were taken twice during the period of immunoglobulin treatment: before the first dose of acid treated (pH 4) immunoglobulin was given, and on the day after the three days of treatment. The first of the two daily doses of antibiotics was always given after blood had been collected. For the control experiments blood was obtained from age matched healthy infants. Serum was prepared by clotting the blood for one hour at room temperature followed by centrifugation for 20 minutes at 1200 *g*, and aliquots were stored at −30°C. Inactivated serum was prepared by heating serum for 30 minutes at 56°C.

Granulocyte enriched cell suspensions were prepared from the blood of healthy adult donors by Dextran sedimentation of the erythrocytes as previously described, and suspended in Hanks's balanced salt solution with 0·1% gelatine to a final concentration of 10^7 cells/ml.[11 12]

S aureus type 42D was cultured overnight at 37°C in nutrient broth (Oxoid), harvested by centrifugation at 1500 *g* for 10 minutes, washed twice with phosphate buffered saline, and resuspended in gelatine and Hanks's balanced salt solution to a concentration of about 10^7 bacteria/ml.[7]

Titration of complement by the classical pathway was performed according to the method of Kabat and Mayer.[13] Serum concentrations of complement C3 and IgG were measured by radial immunodiffusion using specific antisera (Human, Budapest). Serum samples prepared before and after infusion of intravenous immunoglobulin were tested individually from each patient.

The opsonic activity of serum was defined as its capacity to promote ingestion of bacteria by granulocytes. One hundred microlitres of a suspension of granulocytes (concentration 10^7/ml) were incubated with an equal volume of a suspension of 10^7 bacteria/ml in various concentrations of serum, and mixed by tumbling (4 rpm) at 37°C. After 60 minutes of phagocytosis, 50 μl aliquots of the mixture were added to 450 μl of ice cold Hanks's balanced salt solution, and cells were pelleted by centrifugation for 6 minutes at 75 *g*. The number of viable extracellular bacteria was determined by microbiological assay.[7] The opsonic activity of serum before and after infusion of intravenous immunoglobulin was determined individually from each infant. The viability of granulocytes after 60 minutes of phagocytosis remained higher than 96% (checked by trypan blue exclusion).

Phagocytosis of *S aureus* by normal human granulocytes at a concentration of 5×10^6/ml at 1:1 bacterium:cell ratio in the presence of fresh or heat inactivated sera from patients was measured before and after a three day treatment with acid treated intravenous immunoglobulin. Serum samples from age matched healthy infants were used in control experiments. Percentages of phagocytosed bacteria were determined by colony counts after 60 minutes incubation (table 3).

An acid treated intravenous immunoglobulin concentrate (Sandoz AG) prepared at pH 4 was administered to the patients by slow infusion in a dose of 250–300 mg/kg daily for three days.

Statistical analysis of the data was carried out by standard methods.[14] The significance of differences was assessed by the unpaired *t* test.

Results

Intravenous immunoglobulin treatment was well tolerated without side effects. All except case 1 recovered from the acute bacterial infection; she died of meconium aspiration followed by septicaemia. Cases 12 and 13 developed hydrocephalus and oesophageal stenosis, respectively. The rest of the treated patients recovered without complications. No clinical signs or symptoms of septic shock were observed.

In the control group of 13 infants (including five neonates) with septicaemia or other severe *S aureus* infections who were given only conventional antibiotic treatment, three patients (cases 1, 3, and 7) died, and one (case 2) recovered with complications. The others recovered from the bacterial infection without complications. Days in hospital, duration of fever, and dosage of antibiotics were all about the same in the two groups. There were no significant differences in time from the onset of symptoms of infection to administration of antimicrobial drugs between study patients and controls (mean (SD) number of days, 2·9 (1·8) compared with 3·2 (2·0).

Before treatment with immunoglobulin was introduced patients' serum opsonised *S aureus* less effectively than serum from age matched controls. After three days of treatment with immunoglobulin, opsonisation of *S aureus* by both fresh and heat inactivated serum increased, and was similar to that of the control values for all serum concentrations tested (table 3). Mean differences, between opsonic values before and after infusion were higher when heat inactivated serum samples were used as a source of opsonins than when fresh serum samples were used (table 3 and 4). This might be explained by the combined effect of complement and immunoglobulins in opsonising *S aureus* in fresh serum. In heat inactivated serum, however, the activity of complement is abolished and opsonisation of bacteria is related mainly to the concentration and functional activity of IgG. Differences between opsonic values in fresh and heat inactivated serum taken before and after intravenous infusion of immunoglobulin were significant (table 4).

Table 3 *Phagocytosis promoting activity of serum from 13 infants with severe sepsis treated with immunoglobulin. Figures are mean (SD) of 13 experiments*

	Concentration of serum (%)	*Percentage phagocytosed bacteria in the presence of patients' sera*		*Control sera*
		Before treatment	*After treatment*	
Incubation of granulocytes and bacteria with:				
Fresh serum	10	72·9 (14·3)	96·8 (6·0)	94·8 (2·9)
	5	72·0 (12·9)	86·7 (10·7)	92·3 (12·5)
	1	58·9 (13·6)	74·7 (9·8)	78·4 (10·7)
Heat inactivated serum	10	22·8 (10·2)	63·5 (14·3)	59·4 (10·4)
	5	21·8 (13·8)	58·1 (12·8)	58·5 (9·2)
	1	7·9 (6·7)	38·2 (12·3)	32·9 (9·9)

Table 4 *Statistical evaluation of the effect of treatment with intravenous immunoglobulin on opsonic activity of serum from 13 infants with severe sepsis*

Concentration (%)	*Mean differences (%)*	*SE of mean differences*	*Confidence intervals (%)*	*p Value*
Fresh serum:				
10	23·9	4·02	15·1 to 32·6	<0·001
5	14·7	4·64	4·6 to 24·8	<0·01
1	15·8	4·65	5·6 to 25·9	<0·01
Heat inactivated serum:				
10	40·8	4·89	30·1 to 51·4	<0·001
5	36·3	5·21	24·9 to 47·7	<0·001
1	30·3	4·09	21·4 to 39·2	<0·001

Table 5 *In vitro growth of S aureus in the presence of heat inactivated sera from 13 infants with severe sepsis treated with immunoglobulin*

Time of serum preparation	*Concentration of serum (%)*	*Mean (SD)% of viable bacteria*
Before treatment:	10	138 (19·2)
	5	130 (18·5)
	1	131 (20·1)
After treatment:	10	129 (17·6)
	5	132 (18·2)
	1	121 (14·8)

The bactericidal activity of serum from the study patients was measured by the in vitro growth of *S aureus* in various concentrations of heat inactivated sera (table 5). Incubation of bacteria without granulocytes in heat inactivated serum showed an increase in the number of micro-organisms, which indicated that there was no bactericidal activity in the samples tested. The number of viable bacteria after 60 minutes' incubation was about the same in the serum samples taken before and after treatment with immunoglobulin (table 5).

Haemolytic activity of the classical complement pathway was not influenced by immunoglobulin treatment (table 6). The same was true for concentrations of complement C3, whereas the serum concentration of IgG was significantly increased by the total of 800–900 mg immunoglobulin given over the three day period.

Discussion

S aureus and other staphylococci cause a diverse group of infections. *S aureus* accounts for more than 10% of nosocomial infections and causes 20% of infections in paediatric wards.[15] Polymorphonuclear neutrophil leucocytes play a key part in the host

Table 6 *Haemolytic activity of complement and concentrations of complement C3 and IgG in serum from infants with severe sepsis treated with immunoglobulin. Figures are mean (SD)*

	Before treatment	*After treatment*	*p Value*
Complement haemolytic activity (U/ml)	37·50 (5·10)	36·20 (3·90)	NS
Complement C3 (g/l)	0·80 (0·15)	0·86 (0·18)	NS
IgG (g/l)	7·70 (1·90)	12·80 (1·80)	<0·01

defence against staphylococci, yet without opsonins they inhibit *S aureus* only to a limited extent.[16] Complement clearly augments inhibition in vitro, but alone it is not impressive.[17] Although the role of specific antibodies in protection against infection with *S aureus* is not completely understood, it is known that IgG is essential to inhibit *S aureus* even at a concentration of 0·25 g/l.[16] Defects in antibody mediated opsonisation can occur as primary deficiencies of immunoglobulin synthesis or can be a consequence of sytemic infection caused by consumption of specific antibodies by the infecting organism.

In this study we found that both IgG mediated and IgG and complement mediated opsonic activity against *S aureus* could be improved in infants with *S aureus* septicaemia by treatment with intravenous immunoglobulin; the infused IgG resulted in functionally increased opsonisation. The presence of specific antibodies in the polyvalent IgG preparations against common bacterial pathogens may explain this. Indeed, the IgG preparations are fractionated from a pool of several thousand blood donations, so that antibodies to endemic pathogens are concentrated and rare antibodies are diluted.

The higher rate of ingestion of *S aureus* by normal granulocytes in fresh serum compared with heat inactivated serum suggested that opsonisation was optimal when complement was functional. These results further emphasise the contributory effect of complement in the opsonisation of micro-organisms. The significant improvement of the opsonic activity of heat inactivated serum after infusion of immunoglobulin could be explained by the action of heat stable opsonins, specific IgG antibodies directed against the given pathogen.

The growth of bacteria in various concentrations of heat inactivated serum taken before treatment was comparable with that in serum taken after treatment with immunoglobulin. This excludes the possibility of improved opsonisation of *S aureus* by the antibiotics that were given at the same time as the immunoglobulin to all the patients.

It is important to point out that the haemolytic activity of complement and concentrations of complement C3 were not significantly influenced by treatment with immunoglobulin. This suggests that administration of high dose immunoglobulin did not result in impairment of complement mediated effector function in septicaemic infants.

These results indicate that treatment with intravenous immunoglobulin may be useful in modifying disease caused by *S aureus* in infants. Further evaluation will require a prospective, controlled study of the use of intravenous immunoglobulin in septicaemic infants in order to determine the real clinical importance of this treatment in the outcome of severe staphylococcal disease. It is necessary to identify groups of infants with severe sepsis in whom treatment with intravenous immunoglobulin might be useful.

References

[1] Bussel JB, Goldman A, Imbach P, Schulman J, Hilgartner MW. Treatment of acute idiopathic thrombocytopenia of childhood with intravenous infusions of gammaglobulin. *J Pediatr* 1985;**106**:886–90.

[2] Calvetti TA, Rubinstein A. Intravenous gamma-globulin in infant acquired immunodeficiency syndrome. *Pediatr Infect Dis* 1986;**5**(suppl):207–10.

[3] Imbach P, Barandun S, d'Apuzzo V. High dose intravenous gamma-globulin for idiopathic thrombocytopenic purpura in childhood. *Lancet* 1981;**i**:1228–31.

[4] Fischer GW, Hemming VG, Hunter KW, *et al*. Intravenous immunoglobulin in the treatment of neonatal sepsis: therapeutic strategies in laboratory studies. *Pediatr Infect Dis* 1986;**5**(suppl):171–5.

[5] von Muralt G, Sidiropoulos D. Experience with intravenous immunoglobulin treatment in neonates and pregnant women. *Vox Sang* 1986;**51**(suppl):22–9.

[6] Johnston RB, Klemperer MR, Alper CA, Rosen FS. The enhancement of bacterial phagocytosis by serum: the role of complement components and two cofactors. *J Exp Med* 1969;**124**:1275–90.

[7] Marodi L, Leijh PCJ, Braat A, Daha M, van Furth R. Opsonic activity of cord blood sera against various species of micro-organisms. *Pediatr Res* 1985;**19**:433–6.

[8] Muller-Eberhard HJ, Schreiber RD. Molecular biology and chemistry of alternative pathway of complement. *Adv Immunol* 1980;**29**:1–35.

[9] van Furth R, Leijh PCJ, Klein F. Correlation between opsonic activity for various micro-organisms and composition of gamma-globulin preparations for intravenous use. *J Infect Dis* 1984;**149**:511–7.

[10] Giver LB, Edwards MS, Anderson DC, Baker CJ. Immune globulin for intravenous use: enhancement of in vitro opsonophagocytic activity of neonatal sera. *J Infect Dis* 1985;**151**:217–20.

[11] van Furth R, van Zwet ThL, Leijh PCJ. In vitro determination of phagocytosis and intracellular killing by polymorphonuclear and mononuclear phagocytes. In: Weir DM, ed. *Handbook of experimental immunology*. 3rd ed. Oxford: Blackwell Scientific, 1978:32.1–32.19.

[12] Marodi L, Leijh PCJ, van Furth R. A micromethod for the separate evaluation of phagocytosis and intracellular killing of Staphylococcus aureus by human granulocytes and monocytes. *J Immunol Methods* 1983;**57**:353–61.

[13] Kabat EA, Mayer MM. *Experimental immunochemistry*. 2nd ed. Springfield: Thomas, 1961:1275–90.

[14] Armitage P. *Statistical methods in medical research*. Oxford: Blackwell, 1971.

[15] Cohen ML. Staphylococcus aureus: biology, mechanisms of virulence, epidemiology. *J Pediatr* 1986;**108**:796–9.

[16] Monteil M, Hobbs J. Selective immunodeficiency affecting staphylococcal response. *Lancet* 1987;**ii**:880–3.

[17] Verburgh HA, van Dijk WC, Erne ME, Peters R, Peterson PK, Verhoef J. Quantitation of the third component of human complement attached to the surface of opsonized bacteria: opsonin-deficient sera and phagocytosis resistent strains. *Infect Immun* 1979;**26**:808–12.

Correspondence to Dr L Marodi, Department of Paediatrics, University Medical School of Debrecen, H-4012 Debrecen, POB:32, Hungary.

Accepted 18 September 1988

Archives of Disease in Childhood, 1989, **64,** 535–540

Intradermal hepatitis B vaccine in thalassaemia and sickle cell disease

Q MOK,* G UNDERHILL,† B WONKE,* M ALDOURI,‡ M KELSEY,* AND D JEFFERIES†

**Whittington, †St Mary's, and ‡the Royal Free Hospitals, London*

SUMMARY Thirty two patients with β thalassaemia and sickle cell disease who were having regular blood transfusions were selected to test the efficacy and immunogenicity of low dose (2 μg or 0·1 ml) intradermal hepatitis B vaccine compared with the standard (20 μg or 1 ml) intramuscular dose. There was no significant difference in the rates of seroconversion, seroconversion had occurred in all patients by seven months. There were no significant differences in antibody titres between the intramuscular and intradermal groups at 1, 2, and 6 months. Although the titres were significantly higher in the intramuscular group at seven months and at 12–18 months, the antibody titre in the intradermal group did not fall below 10 IU/l. The results of this study suggest that low dose intradermal hepatitis B vaccination is an effective and economical way of stimulating an immune response in patients with β thalassaemia and sickle cell disease.

Blood transfusion is still a common mode of transmission of viral hepatitis, and so patients with β thalassaemia and homozygous sickle cell disease who require regular blood transfusions constitute a high risk group. This risk is accentuated in affected children as their need for transfusions begins early in their first year of life and persists into adulthood. Although a group in the United States reported a low incidence of hepatitis B after blood transfusions in patients with thalassaemia,[1] a study in London and Athens[2] has indicated that it remains a serious problem. Vaccination against hepatitis B is a safe and effective way of preventing hepatitis B virus infection.[3-9] The recommended method of immunisation is by a course of three intramuscular injections into the deltoid muscle of 0·5–1·0 ml vaccine at 0, one, and six months. The high cost of the vaccine (£27.15 to £36.21 in 1988), however, has restricted its use, especially in developing countries where hepatitis is endemic and thalassaemia and sickle cell disease are common.

Low dose intradermal administration has been successfully assessed in healthy adult volunteers and health workers ,[10-15] but we know of few reports of this method of vaccination against hepatitis B being used in children and young adults. No study on low dose vaccination of patients with β thalassaemia or sickle cell disease has been reported to our knowledge. The immunological response in these patients may be different, as shown by their increased susceptibility to infections especially after splenectomy (either from autoinfarction in patients with sickle cell disease or surgical splenectomy in patients with thalassaemia).[16-20]

The aim of this study was to investigate whether low dose intradermal hepatitis B vaccination was as effective as vaccination by the standard intramuscular route in provoking an immune response against the hepatitis B virus in patients with thalassaemia and sickle cell disease.

Patients and methods

PATIENTS AND STUDY DESIGN

Thirty two patients who required transfusions of packed cells every two to four weeks were selected for this study. They were all negative for hepatitis B surface antigen (HBsAg), antibody to surface antigen (anti-HBs), and antibody to core antigen (anti-HBc). Twenty eight patients had β thalassaemia (26 β thalassaemia major, and two sickle thalassaemia) and four had homozygous sickle cell disease. There were 16 boys and 16 girls of Greek, Turkish, Indian, or West Indian origin, but they were all born in Britain and received all their transfusions in this country. To prevent and treat transfusional iron overload all the patients received regular subcutaneous desferrioxamine infusions for a period of one to nine years. The iron concentration was monitored at three monthly intervals by measuring the serum ferritin concentration. Liver function tests were also assayed at six monthly intervals for the period of the study.

The study was prospective and the 32 patients were paired for diagnosis, sex (except for pairs 14 and 16), age, serum ferritin concentration, amount of blood transfused, and whether they had had a splenectomy (except for pairs 3 and 11) (table 1).

One member of each pair was given the standard 0·5–1·0 ml (10–20 μg) of plasma derived hepatitis B vaccine (H-B-Vax) intramuscularly into the deltoid muscle. The other member of the pair was given 0·1 ml (2 μg) of the vaccine intradermally into the flexor surface of the forearm. A visible cutaneous bleb indicated a successful intradermal injection. All the vaccinations were performed by the same nursing sister or one of the authors (QM or BW) using a 1 ml tuberculin syringe and a 27 gauge needle. The regimen comprised three doses at 0, one, and six months. Blood was taken for serological assay at 0, one, two, six, seven, and 12–18 months after the initial vaccination. The Wilcoxon signed rank test was used to calculate the significance of differences in the antibody titres between the two groups. The study was approved by the hospital medical ethical committee, and signed consent was obtained.

LABORATORY TESTS

All serum samples for serological examination were stored at −20°C. Samples taken at time 0 were tested for HBsAg, anti-HBc and anti-HBs to give base line values using commercially available enzyme linked immunosorbent assays (Auszyme, Corzyme, and Ausab, respectively). Samples taken at one, two, six, seven, and 12–18 months were tested for anti-HBs, and the amount of surface antibody was determined by diluting them in negative control serum (Abbott Laboratories) until a titre was obtained using the Abbott semiquantitative assay. Results are expressed in IU/l. Seroconversion was taken to have occurred when anti-HBs reached a titre of more than 10 IU/l. Samples taken at the end of the study were also tested for HBsAg and anti-HBc to see if infection with hepatitis B virus had occurred during the study.

Serum ferritin concentration was measured by immunoradiometric assay[21]; the normal ranges for our laboratory are 39–340 μg/l for boys and 14–148 μg/l for girls.

Liver function tests were measured by the standard method of analysis. The normal value for aspartate transaminase is 40 IU/l and for γ-glutamyl transpeptidase 8–50 IU/l.

Six of the patients had persistently raised aspartate transaminase or γ-glutamyl transpeptidase concentrations at the start of the study; four were in the intradermal and two in the intramuscular group. They were seronegative for HBsAg, anti-HBs, and anti-HBc. Liver biopsy specimens were available for these patients,[22] but no hepatitis B surface or core antigen were detected, and the abnormal liver function was thought to be due to non-A non-B hepatitis or to iron overload. The remaining patients had normal liver function tests throughout the study.

Table 1 *Details of patients at start of study*

	Intramuscular group (n=16) Median (range)	*Intradermal group (n=16) Median (range)*
Age (years)	16·9 (1·4–25·4)	16·0 (1·2–23·8)
No of units of blood transfused	295 (15–420)	275 (17–573)
Serum ferritin concentration (μg/l)	800 (380–2160)	850 (180–31[illegible]0)

Results

The only side effects after intradermal injection were transient induration, and in negroid patients hyperpigmentation at the site of injection that faded within a few months.

Seroconversion had occurred in every patient by seven months. The seroconversion rates after the first, second, and third doses are shown in fig 1. Seroconversion had occurred in all the patients in the intramuscular group by six months, before the third dose was given. Titres of anti-HBs are shown in fig 2. At one, two, and six months there were no

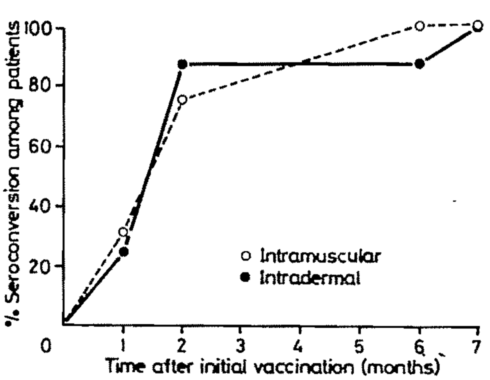


Fig 1 *Seroconversion rates in intramuscular and intradermal groups after vaccination with H-B-Vax.*

significant differences between the two groups, but by seven months the titres were higher in the intramuscular group ($p<0{\cdot}01$). At 12–18 months after the initial vaccination the antibody titres had fallen in both groups, but were significantly lower in the intradermal group ($p<0{\cdot}01$). No patient had a titre below 10 IU/l, however, that would have been considered seronegative.

Table 2 shows some of the details about the patients and the antibody titres achieved. There were seven patients with high serum ferritin concentrations (greater than 1000 μg/l); these were the less compliant patients who used desferrioxamine less regularly than the other patients in the study. Of these patients, four also had abnormal liver function tests.

Within the low dose intradermal group of patients, four had abnormal liver function tests. These patients achieved significantly lower antibody titres (indicated by arrows in fig 2) than the patients with normal liver function tests within the group. The Wilcoxon rank sum test showed significant differences at two months ($p<0{\cdot}05$), six months ($p<0{\cdot}01$), seven months ($p<0{\cdot}05$), and 12–18 months ($p<0{\cdot}005$). There did not appear to be a correlation between splenectomy and degree of antibody response.

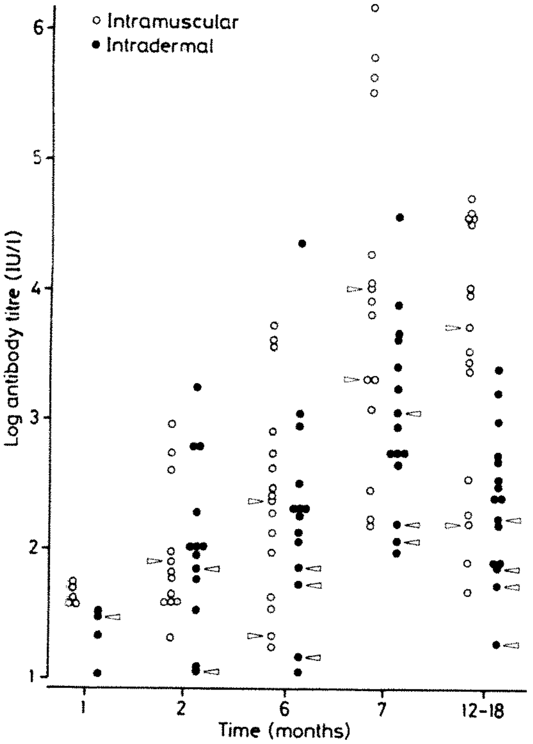


Fig 2 *Titres of antibody to hepatitis B surface antigen as a function of time after initial vaccination. Arrows indicate patients with abnormal liver function. Only titres above 10 IU/l are plotted as this is the minimum activity indicating positive seroconversion.*

Of the 14 patients who had been followed up for two years at the time of writing, 12 continue to show titres ranging from 51 to 21 540 IU/l. In only one patient (from the intramuscular group) was the titre undetectable, and one from the intradermal group had a titre of 12 IU/l. Both these patients had poor antibody responses during the study, their highest titres being 191 and 116 IU/l, respectively.

All patients remained seronegative for anti-HBc and HBsAg at the end of the study, confirming that none had contracted natural hepatitis B infection.

Discussion

Hepatitis is a common complication of blood transfusions,[23 24] although most of the cases are non-A, non-B hepatitis. World wide hepatitis B remains the most important cause, as it may lead to chronic hepatitis and cirrhosis. There is also a strong association between long term carriage of hepatitis B virus and hepatocellular carcinoma.[25–30]

The incidence of hepatitis B virus infection is increasing in Britain[31] where 2–4% of the normal population have serological evidence of exposure to hepatitis B virus, and at least 0·1% remain carriers.[32] Routine screening for hepatitis B surface antigen in donated blood was introduced in Britain in 1971. Nevertheless, 1–3% of donors have antibody to the core antigen as their sole marker of hepatitis B virus infection[33] and may therefore transmit the virus by blood transfusion.[34 35]

The results of this study have shown that a low dose (2 μg) intradermal hepatitis B vaccination can stimulate a humoral immune response comparable with the standard (20 μg) intramuscular dose in patients with β thalassaemia and homozygous sickle cell disease whose immunological responses are thought to be compromised.[16–20] Seroconversion had occurred in all patients by the end of the course of three injections, which is comparable with the results of other studies of healthy volunteers with intramuscular or intradermal vaccine. In the original trials that tested the efficacy of intramuscular hepatitis vaccination, seroconversion occurred in 85 to 100%.[4–8] A few trials of the intradermal vaccination were conducted in healthy adults with similar seroconversion rates (83 to 100%).[10–15] Miller *et al* reported that seroconversion occurred in 83% of 14 healthy adult volunteers,[10] and Zoulek *et al* reported that seroconversion occurred in all of a smaller group of nine healthy adults.[11 12]

Table 2 *Details of patients and titres of antibody to hepatitis B surface antigen*

Details of patients						*Titres of antibody to hepatitis B surface antigen (IU/l) at time intervals (months) initial vaccination*				
Pair No	*Route*	*Diagnosis*	*Ferritin (µg/l)*	*Liver function tests*	*Splenectomy*	*1*	*2*	*6*	*7*	*12–18*
1	Intramuscular	Thalassaemia	950	Normal	Yes	0	43	34	6740	2470
	Intradermal	Thalassaemia	900	Abnormal	Yes	0	67	14	116	17
2	Intramuscular	Thalassaemia	660	Normal	No	56	92	840	19 500	3600
	Intradermal	Thalassaemia	580	Normal	No	0	59	115	92	2400
3	Intramuscular	Thalassaemia	640	Normal	No	38	37	412	688 000	37 800
	Intradermal	Thalassaemia	640	Normal	Yes	0	33	10	1870	235
4	Intramuscular	Thalassaemia	640	Normal	Yes	0	0	42	292	77
	Intradermal	Thalassaemia	610	Normal	Yes	7	1796	137	4020	1600
5	Intramuscular	Thalassaemia	740	Normal	Yes	0	5	91	2140	345
	Intradermal	Thalassaemia	1800	Abnormal	Yes	0	11	70	1160	50
6	Intramuscular	Thalassaemia	840	Normal	No	38	38	1410	1 619 200	37 500
	Intradermal	Thalassaemia	800	Normal	No	32	630	1200	460	481
7	Intramuscular	Thalassaemia	2160	Abnormal	Yes	0	80	240	10 800	5350
	Intradermal	Thalassaemia	1040	Normal	yes	0	12	208	900	73
8	Intramuscular	Thalassaemia	920	Normal	yes	42	65	1540	11 280	9300
	Intradermal	Thalassaemia	1400	Normal	Yes	21	106	205	2650	240
9	Intramuscular	Thalassaemia	600	Normal	Yes	0	60	298	440 800	42 200
	Intradermal	Thalassaemia	650	Normal	Yes	5	105	24 320	520	291
10	Intramuscular	Thalassaemia	900	Normal	Yes	0	0	191	174	46
	Intradermal	Thalassaemia	680	Normal	Yes	8	213	206	7740	500
11	Intramuscular	Thalassaemia	380	Normal	No	3	558	555	337 200	11 100
	Intradermal	Thalassaemia	180	Normal	Yes	5	104	337	4820	940
12	Intramuscular	Thalassaemia	760	Abnormal	Yes	0	0	20	2050	160
	Intradermal	Thalassaemia	2100	Normal	Yes	11	608	920	550	145
13	Intramuscular	Thalassaemia	920	Normal	Yes	0	37	134	8040	33 600
	Intradermal	Thalassaemia	3100	Abnormal	Yes	0	0	5	155	68
14	Intramuscular	Sickle thalassaemia	520	Normal	Yes	3	425	267	151	59 000
	Intradermal	Sickle thalassaemia	1000	Normal	Yes	0	88	180	582	74
15	Intramuscular	Sickle cell disease	880	Normal	Autosplenectomy	52	925	1390	0	2950
	Intradermal	Sickle cell disease	600	Normal	Autosplenectomy	0	0	0	37 680	300
16	Intramuscular	Sickle cell disease	1000	Normal	Autosplenectomy	0	20	17	1314	184
	Intradermal	Sickle cell disease	1420	Abnormal	Autosplenectomy	28	0	52	0	156

Redfield *et al* carried out a trial in which they compared the vaccine given intramuscularly and intradermally to a group of 50 healthy army volunteers; seroconversion occurred in 96% in the intradermal group compared with 100% in the intramuscular group.[13 14] A preliminary report on the use of intradermal vaccine in 604 hospital personnel in Indonesia by Prasetya *et al* showed that seroconversion occurred in 90%.[15] In the present study good seroconversion rates with both the intramuscular and intradermal methods were achieved in a group of patients whose B cell function and immune state were in question. It is likely that this higher rate of seroconversion is the result of the lower age of our groups, as children have better antigenic responses to immunisation than adults.

The anti-HBs titres obtained were not significantly different at one, two, and six months, but were significantly lower at seven and 12–18 months in the intradermal group. Several studies have shown that the risk of hepatitis B virus infection increases as antibody titres decline, and it is closely associated with the persistence of minimum titres of antibody.[36–39] This implies that the protective effect after intradermal vaccination may not last as long as that after intramuscular vaccination. At 12–18 months none of the patients had anti-HBs titres below 10 IU/l, which is the currently accepted minimal protective titre. It has therefore been suggested that patients who have had the intradermal vaccine should be revaccinated earlier than the currently recommended five year interval. We are continuing to monitor antibody titres among these patients. Those with abnormal liver function tests may need to be monitored more closely if they are given the low dose intradermal vaccine, as our data show that they had a significantly lower antibody response.

The objection that may be raised against using intradermal hepatitis vacccination on a large scale is the skill that is required to avoid administering the injection subcutaneously; the results of a recent study among haemophiliacs, however, showed effective rates of seroconversion even with vaccine administered subcutaneously (Miller EJ, Lee CA, Karayiannis P, Holmes S, Thomas HC, Kernoff PBA. Evaluation of subcutaneous and intradermal hepatitis B vaccination in patients with haemophilia. Presented at the British Society for Haematology annual meeting, 1987).

The more widespread use of hepatitis B vaccine is restricted by the current high cost of a course of intramuscular injections. The 10 fold reduction in cost and the proved immunogenicity of the intradermal route of administration of vaccine in patients with β thalassaemia and homozygous sickle cell disease may encourage its more widespread use in the developing world.

This was only a small pilot study of 32 patients, and a much more extensive study is required to confirm the efficacy in patients with β thalassaemia and sickle cell disease.

We thank Mrs S Ahmet for a grant towards this project. We are also grateful to Miss M Laulicht (department of haematology, Royal Free Hospital) for help with measuring the ferritin concentrations, Miss N Shah (department of virology, St Mary's Hospital) for technical help with the immunoassays, and Sister J Kavanagh for carrying out the vaccinations.

References

[1] Pearson HA, Wood C, Andiman W, Bore J, Rink L. Low risk of hepatitis B from blood transfusions in thalassemic patients in Connecticut. *J Pediatr* 1986;**108**:252–3.

[2] Mieli-Vergani G, Vergani D, White Y, *et al.* Hepatitis B virus infection in thalassaemia major treated in London and Athens. *Br Med J* 1984;**228**:1804.

[3] Blumberg BS, Millman I. *Vaccine against viral hepatitis and process.* Patent No 36 36 191. Washington DC: United States Patent Office, 1972.

[4] Szmuness W, Stevens CE, Harley EJ, *et al.* Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high risk population in the United States. *N Engl J Med* 1980;**303**: 833–41.

[5] Szmuness W, Stevens CE, Harley EJ, *et al.* The immune response of healthy adults to a reduced dose of hepatitis B vaccine. *J Med Virol* 1981;**8**:123–9.

[6] Krugman S, Holley HP Jr, Davidson M, Simberkoff MS, Matsaniatis N. Immunogenic effect of inactivated hepatitis B vaccine: comparison of 20 μg and 40 μg doses. *J Med Virol* 1981;**8**:119–21.

[7] Francis DP, Hadler SC, Thompson SE, *et al.* The prevention of hepatitis B with vaccine: report of Centers for Disease Control multicentre efficacy trial among homosexual men. *Ann Intern Med* 1982;**97**:362–6.

[8] Papaevangelou G, Roumeliitou-Karayannis A, Vissoulis CH, *et al.* Reduction of the dose of hepatitis B vaccine. *J Infect* 1983;7(suppl):53–5.

[9] Hepatitis B virus vaccine safety: report of an interagency group. *MMWR* 1982;**31**:465–7.

[10] Miller KD, Gibbs RD, Mulligan MM, Nutman TB, Francis D. Intradermal hepatitis B virus vaccine: immunogenicity and side effects in adults. *Lancet* 1983;**ii**:1454–6.

[11] Zoulek G, Lorbeer B, Jilg W, Deinhardt F. Antibody responses and skin reactivity after intradermal hepatitis B virus vaccine. *Lancet* 1984;**i**:568.

[12] Zoulek G, Lorbeer B, Jilg W, Deinhardt F. Evaluation of a reduced dose of hepatitis B vaccine administered intradermally. *J Med Virol* 1984;**14**:27–32.

[13] Redfield RR, Innis BL, Cannon HG, McNair-Scott R, Bancroft WH. Immunogenicity and reactogenicity of low-dose intradermally administered heptavax-B-vaccine in man. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. *Viral hepatitis and liver disease.* Orlando: Grune and Stratton, 1984:694–5.

[14] Redfield RR, Innis BL, McNair-Scott R, Cannon HG, Bancroft WH. Clinical evaluation of low dose intradermally administered hepatitis B virus vaccine. A cost reduction strategy. *JAMA* 1985;**254**:3203–6.

[15] Prasetya E, Linggadjaja W, Syambali R, Kusumo S, Dharmesetyawan DF, Rahardja U. Intradermal vaccination against hepatitis B in Immanuel Hospital personnel—a preliminary report. *Ann Acad Med Singapore* 1986;**15**:153–7.

[16] Constantoulakis M, Trichopoulos D, Argoustaki O, Economidou J. Serum immunoglobulin concentrations before and after splenectomy in patients with homozygous β thalassaemia. *J Clin Pathol* 1978;**31**:546–50.

[17] Millard RE, Banarjee DK. Changes in T and B blood lymphocytes after splenectomy. *J Clin Pathol* 1979;**32**:1045–9.

[18] Khan AJ, Lee CK, Wolff JA, Chang H, Khan P, Evans HE. Defects of neutrophil chemotaxis and random migration in thalassemia major. *Pediatrics* 1977;**60**:349–51.

[19] Giuntoli JMT, Estevez ME, Sen L, Penalver JA. Defective function of the peripheral blood neutrophils in thalassemia major. *Am J Pediatr Hematol Oncol* 1984;**6**:215–16.

[20] Di Padova F, Durig M, Harder F, Di Padova C, Zanussi C. Impaired antipneumococcal antibody production in patients without spleens. *Br Med J* 1985;**290**:14–6

[21] Addison GM, Beamish MR, Hales CN, Hodgkins M, Jacobs A, Llewellyn P. An immunoradiometric assay for ferritin in the serum of normal subjects and patients with iron deficiency and iron overload. *J Clin Pathol* 1972;**25**:326–9.

[22] Aldouri MA, Wonke B, Hoffbrand V, *et al.* Hepatitis pathology in regularly transfused β thalassaemia major patients on long term subcutaneous desferrioxamine therapy: the role of parentally transmitted hepatitis. *J Clin Pathol* 1987;**40**:1353–9.

[23] Aach RD, Lander JJ, Sherman LA, *et al.* Transfusion-transmitted viruses: interim analysis of hepatitis among transfused and non-transfused patients. In: Vyas GN, Cohen SN, Schmid R, eds. *Viral hepatitis.* San Francisco: Franklin Institute Press, 1978:383–96.

[24] Barbara JAJ, Briggs M. Post-transfusion hepatitis in north London in 1981: a review including a case of hepatitis A. In: Hopkins R, Field SE, eds. *Proceedings of hepatitis workshop, Stirling.* Edinburgh: Nuclear Enterprises, 1982:31–5.

[25] Szmuness W. Hepatocellular carcinoma and the hepatitis B virus: evidence for a causal association. *Prog Med Virol* 1978;**24**:40–69.

[26] Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus. *Lancet* 1981;**ii**:1129–33.

[27] Beasley RP. Hepatitis B virus as the etiological agent in hepatocellular carcinoma—epidemiological considerations. *Hepatology* 1982;**2**:21–68.

[28] Arthur MJP, Hall AJ, Wright R. Hepatocellular carcinoma, and strategies for prevention. *Lancet* 1984;**i**:507–10.

[29] Beasley RP, Hwang LY. Epidemiology of hepatocellular carcinoma. In: Vyas GN, Dienstag JL, Hoofnagle JH, eds. *Viral hepatitis and liver disease.* Orlando: Grune and Stratton, 1984:209–24.

[30] Hall AJ, Winter PD, Wright R. Mortality of hepatitis B positive blood donors in England and Wales. *Lancet* 1985;**i**:91–3.

[31] Polakoff S. Acute viral hepatitis B. Laboratory reports 1980–84. *Br Med J* 1986;**293**:37–8.

[32] Finch R. Time for action on hepatitis B immunisation. *Br Med J* 1987;**294**:197–8.

[33] Tedder RS, Cameron CH, Wilson-Croome R, Howell DR, Colgrove A, Barbara JAJ. Contrasting patterns and frequency of antibodies to the surface, core and envelope antigens of hepatitis B virus in blood donors and in homosexual patients. *J Med Virol* 1980;**6**:323–32.

[34] Hoofnagle JH, Seeff LB, Bales ZB, *et al.* Type B hepatitis after transfusion with blood containing antibody to hepatitis B core antigen. *N Engl J Med* 1978;**298**:1379–83.

[35] Katchaki JN, Bronwer R, Siem TH. Anti-HBc and blood infectivity. *N Engl J Med* 1978;**298**:1422.

[36] Hadler SC, Francis DP, Maynard JF, *et al.* Long term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. *N Engl J Med* 1986;**315**:209–14.

[37] Zachoval R, Jilg W, Lorbeer B, Schmidt M, Deinhardt F. Passive active immunisation against hepatitis B. *J Infect Dis* 1984;**150**:112–7.

[38] Jilg W, Schmidt M, Deinhardt F, Zachoral R. Hepatitis B vaccination: how long does protection last? *Lancet* 1984;**ii**:458.

[39] Zoulek G, Lorbeer B, Jilg W, Deinhardt F. Persistence of anti-HBs after intradermal inoculation of reduced doses of hepatitis B vaccine. *Lancet* 1984;**ii**:983–4.

Correspondence to Dr B Wonke, Department of Haematology, Whittington Hospital, Highgate Hill, London N19 5NF.

Accepted 17 October 1988

Archives of Disease in Childhood, 1989, **64,** 541–545

Newborn splenic volumes vary under different malaria endemic conditions

J A CORKILL,* B J BRABIN,† D F MACGREGOR,‡ M P ALPERS,† AND R D G MILNER*

**Department of Paediatrics, University of Sheffield, Children's Hospital, Sheffield, †Papua New Guinea Institute of Medical Research, Madang, and ‡Goroka Base Hospital, Eastern Highlands Province, Papua New Guinea*

SUMMARY Ultrasound was used to measure newborn splenic dimensions and calculate the volumes in a malarious and a non-malarious region of Papua New Guinea. The median splenic volume of infants born in Madang, where malaria transmission is high throughout the year, was 5·2 cm^3/kg, while that of infants born in Goroka, where malaria is not endemic, was 2·6 cm^3/kg. The cause of this difference is unknown, but possible explanations include fetal exposure to malaria antigens in utero and the high incidence of inherited red cell disorders in the malarious regions of Papua New Guinea.

In 1956 Bruce-Chwatt reported that the mean spleen weight of newborn African infants was one and a half times greater than that of European infants.[1] An association with holoendemic malaria was suggested, and as congenital malaria is rare, it was hypothesised that parasite antigens or specific fractions of maternal antibody could cross the placenta to cause stimulation and proliferation of the fetal spleen. More recently, the offspring of mice infected with *Plasmodium berghei* were shown to have increased spleen to body weight ratios compared with controls.[2] Splenic enlargement occurred without fetal parasitaemia, and the authors postulated that transplacental passage of soluble malaria antigens may occur.

These two studies, both using postmortem findings, suggest that fetal spleen size may be increased in association with maternal malaria. To our knowledge, there are no data on newborn spleen size in live infants born under different malaria endemic conditions. Clinical examination is inadequate for detecting mild degrees of splenomegaly, but recently ultrasound has been used successfully to estimate splenic volume in neonates.[3]

The aim of this study was to measure newborn splenic volumes in Papua New Guinea using ultrasound, and to compare results from a coastal region with year round malaria transmission with those from a highland region where malaria is not endemic. Cord sera were collected to measure concentrations of total IgM and malaria specific IgM, as an indicator of prenatal antigenic stimulation, and passively acquired malaria specific IgG, as an indicator of maternal malaria experience. In Madang, cord and maternal haematological indices were also studied.

Subjects and methods

SUBJECTS

Splenic volumes were measured on singleton infants born at 37–41 weeks' gestation at Madang General Hospital and Goroka Base Hospital. Gestational age was assessed by the method of Dubowitz *et al.*[4] Approval was obtained from the local ethical committee and the mother's permission was sought to measure the baby's spleen.

STUDY AREAS

Madang is on the north coast of Papua New Guinea in an area with a high level of malaria transmission throughout the year. The overall prevalence of malaria in rural Madang varies from 35% to 43% (all species, all ages) the contribution by each species being *P falciparum* 70%, *P vivax* 25%, and *P malariae* 5%.[5] In urban Madang, malaria incidence is lower due to decreased vector transmission and improved access to health services. Goroka is in the Eastern Highlands Province at an altitude of 1650 metres. Early studies found no evidence of malaria in this region, but it now occurs sporadically as a result of development and increased communication with coastal areas.[6]

SPLENIC VOLUME MEASUREMENTS

The ultrasonic apparatus used in both hospitals was a Toshiba Sonolayergraph SAL-22A (Toshiba Corporation, Japan), which is a real time linear scanner with a 3·5 MHz transducer and distance caliper. The calibration was checked before starting the study. Ultrasonography was carried out within 24 hours of birth.

To estimate splenic volume, the infant was placed in the right lateral position, and the spleen visualised in the left upper quadrant. After adjustment to give the optically largest section area in the longitudinal and transverse plane, the organ was measured as length (L) and depth (D_L), and breadth (B) and depth (D_B). The splenic volume was calculated using the volume formula for an ellipsoid:

$$\text{Splenic volume}=0{\cdot}523L\times B\times\frac{D_L+D_B}{2}\ (\text{cm}^3)$$

BLOOD SAMPLING AND LABORATORY PROCEDURES

Cord blood samples were obtained immediately after delivery of the placenta. Serum was separated by centrifugation, and stored at −40°C until analysed. Thick and thin blood films were prepared from maternal peripheral blood, placental blood, and cord blood. These were examined for malaria parasites after staining with Giemsa. Cord serum total IgM concentrations were measured by single radial immunodiffusion using commercial goat antiserum to human IgM and a World Health Organisation reference serum.[7] The lower limit of detectability was 0·02 g/l. Malaria specific IgG and IgM concentrations were measured by an enzyme linked immunoadsorbent assay (ELISA) technique using a sonicate of *P falciparum* infected red blood cells as the malaria antigen.[8]

In Madang, cord and maternal blood samples were also collected in tubes coated with edetic acid. The haemoglobin concentration was estimated by the cyanomethaemoglobin method, the haematocrit by a microhaematocrit method, and the mean corpuscular haemoglobin concentration was calculated.

DATA FROM POSTMORTEM EXAMINATION

In order to obtain an estimation of normal spleen size, the spleen weights of 48 infants who were stillborn or died within 24 hours of delivery were recorded from the Sheffield Children's Hospital postmortem book. The specific gravity of splenic tissue is approximately one (by Archimedes principle), therefore the splenic weight gives an approximate estimation of splenic volume.

STATISTICAL METHODS

The Student's *t* test was used for comparison of means, and the Mann-Whitney test for comparison of medians. Correlation coefficients were estimated by linear regression.

Results

Splenic volume measurements were obtained from 20 infants in Madang and 41 infants in Goroka. The frequency distributions of splenic volume/kg birth weight are shown in the figure. The Goroka distribution is concentrated towards lower values compared with the Madang distribution, with little overlap. The median splenic volumes, lengths, breadths, and depths and interquartile ranges are shown in the table. The median splenic volume from Madang was double that from Goroka (Mann-Whitney test, p<0·0001). No infant had a palpable

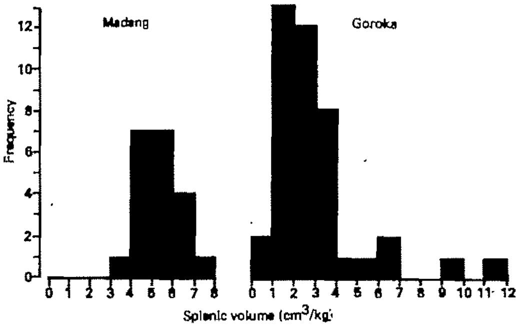


Figure *Frequency distribution of splenic volume/kg birth weight.*

Table *Median splenic volume, length, breadth, and depth (interquartile range in parentheses)*

Source	*No of infants*	*Splenic volume (cm³)*	*Splenic volume/ kg birth weight (cm³/kg)*	*Splenic length (mm)*	*Splenic breadth (mm)*	*Splenic depth (mm)*
Madang*	20	14·5 (13·3–18·3)	5·2 (4·6–6·0)*	40 (36–45)	32 (29–35)	24 (21–25)
Goroka*	41	7·7 (4·3–10·8)	2·6 ([illegible]·5–3·5)	37 (32–42)	22 (17–30)	16 (14–21)
Sheffield†	48	6·5 (3·6–10·5)	2·8 ([illegible]·9–3·6)			

*Mann-Whitney test, p<0·0001; †data from postmortem examination.

spleen nor clinical evidence of perinatal infection. Median splenic volume measurements did not differ in offspring born of primigravidae and multigravidae, and no difference was observed in values from neonates who were small for gestational age and appropriate for gestational age. The mean birth weight in Madang was 3050 g compared with 3120 g in Goroka.

Cord sera were collected from 20 infants in Madang, and 22 out of 41 infants in Goroka. Small amounts of IgM were detected in all samples. The median cord serum total IgM concentration from Madang was 0·045 g/l (interquartile range 0·034–0·057); this was not significantly different from that from Goroka: 0·052 g/l (interquartile range: 0·041–0·065). Splenic volume per kg body weight was negatively associated with cord serum total IgM concentration but the correlation was not significant in Madang or Goroka. All 20 cord sera from Madang were seropositive for malaria specific IgG, compared with two out of 22 cord sera from Goroka. No cord serum was positive for malaria specific IgM antibody. Maternal parasitaemia was found in two cases from Goroka, and five from Madang. No cord blood sample had demonstrable parasitaemia. The splenic volumes of the offspring of parasitised mothers were not significantly different from those of uninfected mothers.

In Madang, the mean (SD) cord haemoglobin concentration was 129 (16) g/l, the mean cord haematocrit was 44 (6·4)%, and the mean cord mean corpuscular haemoglobin concentration was 297 (19) g/l. The mean maternal haemoglobin concentration was 104 (22) g/l, the mean maternal haematocrit was 35 (4·5)%, and the mean maternal mean corpuscular haemoglobin concentration was 306 (27) g/l.

When the different haematological variables were compared with newborn splenic volume there was a significant positive correlation only for cord haemoglobin ($r=0{\cdot}45$, $p<0{\cdot}05$).

Discussion

The main finding of this study was that newborns from a malarious coastal region of Papua New Guinea have significantly larger spleens than those from a non-malarious highland region. Comparison with British data from postmortem examinations suggests that the highland infants have normal spleens, whereas the coastal infants have subclinical splenomegaly.

Measurements in Goroka were made by DFM and in Madang by JAC. Circumstances made it impossible to assess interobserver variation, so we cannot entirely exclude the possibility that the observed difference in splenic volumes was due to interobserver error. Identical techniques of measurement were used in the two centres, however, a clear outline of the spleen was obtained, and as splenic measurements from Madang were enlarged in every dimension compared with those from Goroka, it is likely that the observations are genuine.

In both hospitals it was routine practice to clamp the umbilical cord within 30 seconds of delivery, so variation in splenic volumes should not be due to differences in blood volume.

We do not know of any other data on spleen size in newborns in Papua New Guinea, but some early clinical studies are of interest. Metselaar reported that 75% of infants in a holoendemic malarious area of West New Guinea (now Irian Jaya) had a palpable spleen in the first three months of life.[9] Mackerras and Aberdeen also commented on the high number of large spleens in very young children on the north coast of Papua New Guinea, and suggested that 'many infants may be born with large spleens'.[10] Clinical splenomegaly was not found in newborns in the present study, even though the median splenic volume in Madang was double that in Goroka. It is generally accepted that the spleen must be twice normal in size to be palpable, but it is unclear whether this refers to length or volume.

The aetiology of newborn splenic enlargement in the coastal region is unclear. The fetal spleen has immunological and haematological functions, so mechanisms in both these categories should be considered. A recent study by Desowitz suggests that maternal malaria may cause stimulation of the fetal immune system.[11] He showed that the *P falciparum* specific blastogenic response of cord blood lymphocytes from infants born in Madang was 4·5 times greater than that of cord blood lymphocytes from infants born in Hawaii where malaria transmission does not occur. Possible mechanisms for immune stimulation include: (a) transplacental passage of soluble malaria antigens; (b) asymptomatic congenital malaria; (c) idioanti-idiotype networking in the fetus after acquiring maternal antiplasmodial IgG antibody; and (d) transfer of maternal lymphocytes and/or activated macrophages. Whether immune stimulation by any of these mechanisms would result in an increase in fetal spleen size is unknown.

In highly endemic malarious regions pregnant women are particularly susceptible to malaria because pregnancy appears to interfere with the immune response to the disease.[12] Five Madang women had parasitaemia at delivery, and all the Mandang cord sera contained passively acquired malaria specific IgG, indicating a high degree of maternal exposure to the disease. Splenic volumes did not differ in the offspring of parasitised and non-parasitised mothers, however, and the four Goroka cases with evidence of maternal malaria infection (two with maternal parasitaemia and two with passively acquired malaria specific IgG) did not have enlarged spleens.

Cord serum total IgM and malaria specific IgM concentrations were measured as a possible indicator of prenatal immune stimulation. No significant difference in total IgM concentration between Madang and Goroka was found, and malaria specific IgM was not detected; however, the high concentration of passively acquired malaria specific IgG in cord serum may interfere with the ELISA for malaria specific IgM. These data do not support the hypothesis that fetal immune stimulation is occurring, but it is possible that splenic enlargement could occur by immunological mechanisms independent of antibody production.

Fetal splenomegaly could also result from haematological mechanisms. Erythropoiesis in the spleen normally ceases before birth, but may resume in certain pathological conditions such as haemolytic anaemia.[13]

In Madang the mean cord haemoglobin concentration was 129 g/l, the mean cord haematocrit was 44%, and the mean cord mean corpuscular haemoglobin concentration was 297 g/l. These values are low in comparison with the normal ranges given for developed countries (cord haemoglobin 135–190 g/l, cord haematocrit 44–64%,[14] and cord mean corpuscular haemoglobin concentration 300–350 g/l[15]). Also a significant correlation was found between the cord haemoglobin concentration and the newborn splenic volume ($r=0\cdot45$, $p<0\cdot05$). It therefore seems plausible that the observed splenomegaly in Madang could be the result of a haematological disturbance leading to haemolysis or an increased need for erythropoiesis, or both. Possible causes for this include inherited red cell disorders and malaria.

The precise pathogenesis of malarial anaemia is uncertain, but it is thought to involve both defective production and increased destruction of red cells,[16] and it has been suggested that the immunological destruction of non-parasitised cells may occur.[17] Soluble malaria antigens may be non-specifically absorbed on to the surface of normal erythrocytes, and binding of antibodies to these antigens may trigger complement or cell dependent effector mechanisms resulting in removal of erythrocytes.[18] Placental transfer of soluble antigens and corresponding maternal antibodies could in this way cause fetal haemolysis and anaemia.

Several inherited red cell disorders are common in malarious areas of Papua New Guinea, particularly α thalassaemia, ovalocytosis, and glucose-6-phosphate dehydrogenase deficiency. In the Eastern Highlands only 9% of individuals were found to have α thalassaemia deletions,[19] but around Madang 97% have the genotype $-\alpha/\alpha\alpha$ or $-\alpha/-\alpha$.[20] The incidence of high frequency hereditary ovalocytosis is between 11–30% in the Madang area but is rare in Highlands.[21] Glucose-6-phosphate dehydrogenase deficiency was found in 10–20% of males in Madang, and in 1% of Eastern Highlands males.[20] These inherited red cell disorders could cause a degree of anaemia in the newborn which might explain the increased splenic volumes found in coastal Papua New Guinea. A study in Polynesians on the influence of α thalassaemia on haematological indices found that the mean cord haemoglobin from α thalassaemia homozygotes (genotype $-\alpha/-\alpha$) was 13 g/l less than that of normal individuals ($p=0\cdot01$), while that of α thalassaemia heterozygotes (genotype $-\alpha/\alpha\alpha$) was 4 g/l less ($p<0\cdot05$).[22] Whether α thalassaemia alone would be sufficient to explain the anaemia and the increased splenic volumes found in Madang is uncertain. Another possibility is that fetal splenic enlargement could occur in association with maternal anaemia by the transplacental passage of a haemopoietic stimulus. Under these circumstances, however, high cord haemoglobin concentrations would be expected rather than the low concentrations found in this study.

Further work should be aimed at confirmation of these findings and differentiation between haematological and immunological causes of newborn splenic enlargement.

JAC wishes to thank the Isle of Man Postgraduate Medical Centre, the Edward Boyle Memorial Trust, the Papua New Guinea Institute of Medical Research, and the Foulkes Foundation for financial support, and Mrs G Darwin for tuition in ultrasonography. DFM wishes to thank the midwives at Goroka Base Hospital for cord blood collections, and Dr J Richens for tuition in ultrasonography. The help of Dr Mohan, Dr C Witt, Mr A Raiko, Dr K Forsyth, and Mrs D Parsons is gratefully acknowledged.

References

[1] Bruce-Chwatt LJ. Biometric study of spleen- and liver-weights in Africans and Europeans, with special reference to endemic malaria. *Bull WHO* 1956;**15**:513–48.

[2] Odoula AMJ, Holbrook TW, Galbraith RM, Bank H, Spicer SS. Effects of malaria (Plasmodium berghei) on the maternal-foetal relationship in mice. *J Protozool* 1982;**29**:77–81.

[3] Dittrich M, Milde S, Dinkel E, Baumann W, Weitzel D. Sonographic biometry of liver and spleen size in childhood. *Pediatr Radiol* 1983;**13**:206–11.

[4] Dubowitz LMB, Dubowitz V, Goldberg C. Clinical assessment of gestational age in the newborn infant. *J Pediatr* 1970;**77**:1–10.

[5] Cattani JA, Tulloch JL, Vrbova H, *et al.* The epidemiology of malaria in a population surrounding Madang, Papua New Guinea. *Am J Trop Med Hyg* 1986;**35**:3–15.

[6] Radford AJ, van Leeuwen H, Christian SH. Social aspects in the changing epidemiology of malaria in the highlands of New Guinea. *Ann Trop Med Parasitol* 1976;**70**:11–23.

[7] Mancini G, Carbonara AO, Heremans JF. Immuno-chemical quantitation of antigens by single radial immunodiffusion. *Immunochemistry* 1965;**2**:235–56.

[8] Voller A, Cornille-Broger R, Storey J, Molineaux L. A longitudinal study of Plasmodium falciparum malaria in the West African savanna using the ELISA technique. *Bull WHO* 1980;**58**:429–38.

[9] Metselaar D. Spleens and holoendemic malaria in West New Guinea. *Bull WHO* 1956;**15**:635–49.

[10] Mackerras IM, Aberdeen JBC. Malaria survey at Wewak, New Guinea. *Med J Aust* 1946;**2**:763–71.

[11] Desowitz RS. Prenatal immune priming in malaria: antigen-specific blastogenesis of cord blood lymphocytes from neonates born in a setting of holoendemic malaria. *Ann Trop Med Parasitol* 1988;**82**:121–6.

[12] Brabin BJ. An analysis of malaria in pregnancy in Africa. *Bull WHO* 1983;**61**:1005–16.

[13] Thompson RB. *Disorders of the blood. A textbook of clinical haematology*. London: Churchill Livingstone, 1977.

[14] Dacie JV, Lewis SM. *Practical haematology*. 5th ed. London: Churchill Livingstone, 1975.

[15] Oski FA, Naiman JL. *Haematologic problems in the newborn*. 3rd ed. New York: WB Saunders Company, 1982.

[16] Weatherall DJ, Abdalla S. The anaemia of Plasmodium falciparum malaria. *Br Med Bull* 1982;**38**:147–51.

[17] Facer Ca, Bray RS, Brown J. Direct Coombs antiglobulin reactions in Gambian children with Plasmodium falciparum malaria. I. Incidence and class specificity. *Clin Exp Immunol* 1979;**31**:119–27.

[18] Ristic M, Abroise-Thomas P, Kreier JP. *Malaria and babesiosis*. Amsterdam: Martinus Nijhoff Publishers, 1984.

[19] Flint J, Hill VS, Bowden DK, *et al.* High frequencies of α-thalassaemia are the result of natural selection by malaria. *Nature* 1986;**321**:744–50.

[20] Yenchitsomanus P, Summers KM, Chockkalingham C, Board PG. Characterisation of G6PD deficiency and thalassaemia in Papua New Guinea. *Papua New Guinea Med J* 1986;**29**:53–8.

[21] Cattani JA, Gibson FD, Alpers MP, Crane GG. Hereditary ovalocytosis and reduced susceptibility to malaria in Papua New Guinea. *Trans R Soc Trop Med Hyg* 1987;**81**:705–9.

[22] Mickleson KNP, Dixon MW, Hill PJ, *et al.* Influence of α-thalassaemia on haematological parameters in Polynesian patients. *NZ Med J* 1986;**98**:1036–8.

Correspondence to Professor RDG Milner, Children's Hospital, Sheffield S10 2TH.

Accepted 24 October 1988

Archives of Disease in Childhood, 1989, **64**, 546–550

Measurement of nasal mucociliary clearance

G M CORBO,* A FORESI,* P BONFITTO,† A MUGNANO,* N AGABITI,† AND P J COLE‡

**Centro Auxologico Italiano, Divisione di Pneumologia Pediatrica, Milan, †Istituto di Clinica Medica, Servizio di Fisiopatologia Respiratoria, Università Cattolica del S Cuore, Rome, Italy, and ‡Host Defence Unit, Cardiothoracic Institute, Brompton Hospital, London*

SUMMARY The saccharin test was carried out in a randomly selected sample of schoolchildren (142 boys and 153 girls, age range 11–14 years) to determine the variability and reproducibility of the test and to assess whether it could be used as a screening test for nasal mucociliary clearance. Nasal mucociliary clearance times were analysed according to clinical history (asthma, rhinitis, asthma with rhinitis, and acute upper respiratory tract infections), laboratory findings (positive skin test responses and bronchial hyper-reactivity assessed by methacholine challenge), and parental smoking. Nasal mucociliary clearance times showed a narrow coefficient of repeatibility (six minutes) in 50 subjects and there was substantial agreement between the two tests. Nasal mucociliary clearance times were less than 40 minutes in all the children. Normal children had nasal mucociliary clearance times of less than 24 minutes while significantly impaired nasal mucociliary clearance was detected in those with positive skin reactions and a positive response to methacholine challenge. We were unable to show that passive smoking had any consistent effect on nasal mucociliary clearance.

We suggest that a time response between 30–60 minutes should be checked again at least two weeks later, and that children in whom repeated saccharin tests show a nasal mucociliary clearance of greater than 30 minutes should have ciliary beat frequency estimated.

Mucociliary clearance is a key defence mechanism in human upper and lower airways, and its impairment, both acquired[1] and genetically determined,[2-3] predisposes to chronic infection of the nose, paranasal sinuses, and respiratory tree. The age of onset of clinical symptoms is usually early but diagnosis is often late, because symptoms are not specific (for example, cough and sputum) and techniques for measurement of mucociliary clearance are time consuming and too expensive for routine screening. There is, however, evidence that mucociliary clearance occurs in the trachea and main bronchi at a similar rate as in the nose and so several simple methods have been developed to measure the nasal mucociliary clearance.[4]

The saccharin test is inexpensive and simple to perform, and its results are similar to those obtained using a radioactively labelled particle.[5] Recently it has been proposed as a screening test to detect abnormal mucociliary clearance.[6] We have used the test to measure nasal mucociliary clearance in a random sample of schoolchildren. The purpose of the present study was to establish the normal range of results and reproducibility of the test in children, and to determine whether acute upper respiratory tract infection (common cold), allergic diseases such as bronchial asthma and rhinitis, clinical bronchial hyper-reactivity and atopy, and exposure to passive smoking, prolonged the nasal mucociliary clearance.

Subjects and methods

SUBJECTS

The study was conducted in Verbania in northern Italy. Two hundred and ninety five schoolchildren, 142 boys and 153 girls, age range 11–14 years, were studied. The group was a 20% sample stratified for age and sex and randomly selected from secondary school records.

Information about respiratory diseases such as asthma and rhinitis was obtained from a questionnaire that was completed by the parents. The smoking habits of mothers and fathers were also recorded. The questionnaire incorporated the American Thoracic Society children's questionnaire[9] expanded to include more detailed questions on allergic diseases. A diary card to complete daily was given to the parents two weeks before the examination, and children who had a common cold during the seven days before the test were defined as having an acute upper respiratory tract infection.

SACCHARIN TEST

The saccharin test was carried out by the method first described by Andersen *et al*[7] and modified by Rutland and Cole.[8] A particle 1 mm in diameter was placed under direct vision on the inferior nasal turbinate 1 cm from its anterior end. The child was instructed not to sniff, sneeze, or cough during the test and to report a taste as soon as it was noted. Subjects who had severe watery rhinorrhoea were excluded. The time to the initial perception of a sweet taste was recorded in minutes. If no taste was apparent after 60 minutes the test was stopped and the ability of the subject to taste saccharin placed directly on the tongue was verified. In 50 children (25 boys and 25 girls) the test was repeated in the same nostril the following day to assess its reproducibility.

ATOPIC STATE AND BRONCHIAL RESPONSIVENESS

Atopic state was assessed by performing skin tests using five commonly inhaled allergens (grass, mugwort, birch, and parietaria, and house dust mite). The details of the skin test technique and the allergen extracts have previously been published.[10] Wheal reactions were measured by a planimeter and a wheal area of 3 mm^2 or greater was recorded as a positive response. Bronchial responsiveness was evaluated by the methacholine test using a standard method.[11] Twelve concentrations (from 0·03 mg/ml up to 64 mg/ml) were given through a DeVilbiss 646 nebuliser attached to a dosimeter (Mefar). A reduction in forced expiratory volume in one second (FEV$_1$) of 20% or more was selected to categorise subjects into responders (in whom the provocative concentration of methacholine needed to reduce the FEV$_1$ by 20% was less than 64 mg/ml), and non-responders (in whom a dose of 64 mg/ml of methacholine failed to reduce the FEV$_1$ by 20%).

STATISTICAL ANALYSIS

Having assessed data from the questionnaires, diary cards, skin test reactions, and the bronchial response to methacholine we divided the sample into eight groups: patients with asthma alone; patients with rhinitis alone; those with asthma and rhinitis; those who had an acute upper respiratory tract infection within the last week; those who had positive reactions to skin tests alone; those who had a positive response to the methacholine challenge alone; those who had positive reactions to both the skin tests and the methacholine challenge; and normal subjects.

Comparisons were made between each of the first seven groups and the normal group separately using the Mann-Whitney U test. Lastly, to assess the effect of parental smoking, the children were grouped by the number of parents who currently smoked. Children whose parents had never smoked were compared separately with those who had one parent or both parents who were currently smokers, also using the Mann-Whitney U test.

Reproducibility was assessed by calculating the difference in nasal mucociliary clearance time between the tests on successive days in each subject and then the mean and standard deviation (SD) of the differences in the overall sample. The 95% coefficient of reproducibility is given as two SD.[12] The interclass correlation coefficient (Ri) was also computed.[13]

Results

In 36 subjects the test was not carried out either because of rhinorrhoea (n=12) or because the child was unwilling (n=24). The median nasal mucociliary clearance as measured by the saccharin test in the remaining 259 children was eight minutes (range 1–40) (fig 1). The difference between the measurements on successive days with respect to the mean in each subject is shown in fig 2. The mean value of the differences (−0·26) was not significantly different from zero.

The computed coeffficient of reproducibility was

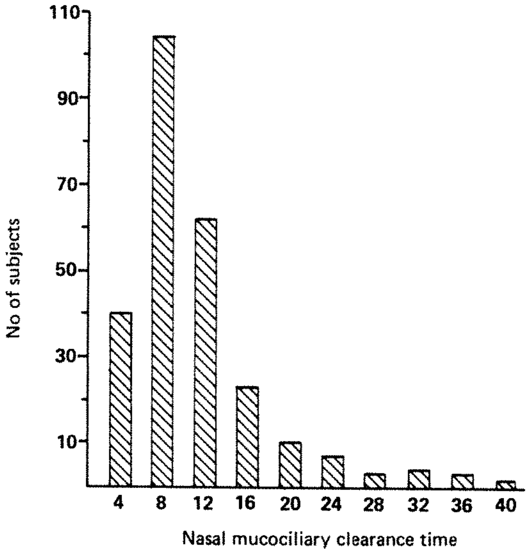


Fig 1 *Nasal mucociliary clearance time measured by the saccharin test in 259 children.*

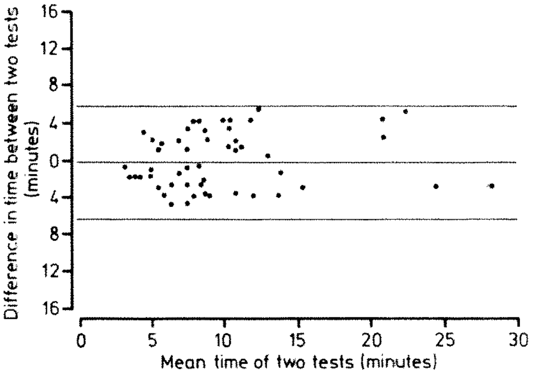


Fig 2 *Mean nasal mucociliary clearance time of two tests plotted against the difference in time between the two tests. Horizontal lines indicate mean and two standard deviations above and below.*

six minutes (2SD).[13] The agreement between the two tests was substantial (Ri=0·80) according to the guidelines of Landis and Kock.[14] When the data from the questionnaire were analysed six children were reported to have asthma without rhinitis, 25 had rhinitis alone, and 10 had both asthma and rhinitis. Forty children had positive reactions to skin tests and did not respond to the methacholine challenge. A reduction in FEV_1 of more than 20% after the methacholine challenge was detected in 20 subjects who did not react to the skin tests, and both positive reactions to skin tests and bronchial responses to the methacholine challenge were found in 20 children (table).

Normal subjects had nasal mucociliary clearance times of less than 24 minutes, while longer times were detected in some subjects in other groups. There were no significant differences between normal children compared with children with asthma, children with rhinitis, children with both asthma and rhinitis, those with positive skin test reactions, those who responded to the methacholine challenge or children with acute upper respiratory infections. Children with colds had longer nasal mucociliary clearance times than normal children though the difference was not significant (p=0·09). A significant reduction in nasal mucociliary clearance was, however, found in those with positive reactions to skin tests and a positive response to the methacholine challenge (z=2·404, p=0·01469).

Ninety eight subjects (38%) had one parent currently smoking, 51 (20%) had both parents currently smoking, and 110 (47%) had parents who had never smoked. There was no significant difference between children whose parents never smoked and children whose parents currently smoked.

Discussion

The results of our study confirm those of Stanley *et al*[6] that the saccharin test is an useful screening technique for measuring nasal mucociliary clearance as it is inexpensive, simple to do, and reproducible, and we have extended their results in adults to children. The nasal mucociliary clearance times found in normal children did not differ from those found by Andersen and Proctor[4] who considered that any time in excess of 30 minutes was abnormal; we did not find any result in excess of 24 minutes.

The test showed a rather narrow coefficient of reproducibility (six minutes, figure) and the mean value of the differences (−0·26) was not significantly different from zero, which means that the first measurement is not affecting the second and the difference does not vary in any systematic way over the range of measurements. The agreement between the two tests was substantial (Ri=0·80).

Nasal mucociliary clearance depends on two principal components, the physiochemical qualities and quantity of the mucus, and the properties of the

Table *Nasal mucociliary clearance times in each group measured by the saccharin test*

Clinical group	*Total No*	*Median (range) clearance time (minutes)*
Normal subjects	98	8 (1–24)
Patients with asthma alone	6	9 (3–36)
Patients with rhinitis alone	25	8 (2–36)
Patients with asthma and rhinitis	10	9 (3–32)
Patients with upper respiratory tract infections	40	9 (1–40)
Patients with positive skin responses alone	40	8 (2–35)
Patients with positive response to methacholine challenge alone	20	7 (2–36)
Patients with positive skin responses and positive response to methacholine challenge	20	10 (3–40)

cilia that propel it (for example, beat frequency and coordination); these are affected by disease. We did, however, find a significantly impaired nasal mucociliary clearance only in children with both positive skin reactions, and a positive response to the methacholine challenge. At present data on mucociliary clearance in allergic diseases are controversial.[15 16] Abnormal mucociliary clearance was seen in patients with bronchial asthma,[17] and abnormal cilia were found in subjects with perennial rhinitis.[18] Impairment of mucociliary clearance in patients with asthma seems to be the result of qualitative[19 20] and quantitative[21] alterations in respiratory secretions rather than differences in ciliary beating.[22] As these changes are transient, the saccharin test may fail to show impairment of nasal mucociliary clearance depending on the time that has elapsed since the exposure to the allergen. We found a prolonged nasal mucociliary clearance time only in subjects with both skin reactivity to allergen extracts and increased bronchial response to methacholine.

Acute upper respiratory tract infections may reduce the nasal mucociliary clearance by direct damage to the cilia and change in the rheological properties of the nasal secretions.[23-25]

Tobacco smoke has a ciliostatic effect[26] and changes the viscoelastic properties of mucus.[27 28] Recently nasal mucociliary clearance time in smokers has been found to be longer than in non-smokers.[29] In the same study the route of exhalation was shown to be crucial, as smokers who regularly exhaled through their noses had a longer mean nasal mucociliary clearance time than smokers who did not regularly exhale by this route. We have not shown any consistent effect of passive smoking on nasal mucociliary clearance, however, probably because the effect is cumulative,[29] and depends on the degree and the duration of exposure (that is, the current amount of parental smoking of cigarettes, number of parental smokers during the child's lifetime, and the duration of parental smoking during child's lifetime).

In conclusion, we have shown that the saccharin test can be used on a large sample to study nasal mucociliary clearance in childhood because it is simple to carry out and the results have a good coefficient of repeatability. We have confirmed that 30 minutes is the cut off point that discriminates normal subjects from subjects with impaired nasal mucociliary clearance. Patients with positive responses to skin tests and increased bronchial reactivity showed a significantly prolonged nasal mucociliary clearance time. We failed to show any differences between the normal group and the other groups, because the range in the results in the various groups was so wide that it was difficult to pick up small differences.

Nevertheless, a time response of more than 30 minutes should be checked again at least two weeks later in case it is due to an acute upper respiratory infection. Lastly, children who have repeated saccharin tests in which they take longer than 30 minutes to respond when they do not have an acute infection need further investigation.

We thank I Annesi and F Kauffmann for their comments and suggestions, and M Lebowitz for his advice.

References

[1] Afzelius BA, Camner P, Mossberg B. Acquired ciliary defects compared to those seen in the immotile-cilia syndrome. *Eur J Respir Dis* 1983;**64:**(suppl 127):5–10.

[2] Sleigh MA. Primary ciliary dyskinesia. *Lancet* 1981;**ii:**476.

[3] Eliasson R, Mossberg B, Camner P, Afzelius BA. The immotile cilia syndrome. A congenital abnormality as an etiologic factor in chronic airway infections and male sterility. *N Engl J Med* 1977;**297:**1–7.

[4] Andersen I, Proctor DF. Measurement of nasal mucociliary clearance. *Eur J Respir Dis* 1983;**64** (suppl 127):37–40.

[5] Andersen IB, Camner P, Jensen PL, Philipson K, Proctor DF. Nasal clearance in monozygotic twins. *Am Rev Respir Dis* 1974;**110:**301–5.

[6] Stanley P, MacWilliam L, Greenstone M, Mackay I, Cole P. Efficacy of a saccharin test for screening to detect abnormal mucociliary clearance. *Br J Dis Chest* 1984;**78:**62–5.

[7] Andersen I, Camner P, Jensen PL, Philipson K, Proctor DF. A comparison nasal and tracheobronchial clearance. *Arch Environ Health* 1974;**29:**290–3.

[8] Rutland J, Cole PJ. Nasal mucociliary clearance and ciliary beat frequency in cystic fibrosis compared with sinusitis and bronchiectasis. *Thorax* 1981;**36:**654–8.

[9] Ferris BG. Epidemiology standardization project: children's questionnaire. *Am Rev Respir Dis* 1978;**118**(suppl):36–53.

[10] Corbo GM, Foresi A, Verga AE, Mattoli S, Polidori G, Ciappi G. Allergy indices based on allergen dose-response curve in a randomly selected sample of schoolchildren. *Allergy* 1987;**42:** 230–7.

[11] Ryan G, Dolovich MB, Roberts RS, *et al.* Standardization of inhalation provocation tests: two techniques of aerosol generation and inhalation compared. *Am Rev Respir Dis* 1981;**123:** 195–9.

[12] Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;**i:**307–10.

[13] Kramer MS, Feinstein AR. Clinical biostatistics. LIV. The biostatistics of concordance. *Clin Pharmacol Ther* 1981;**29:** 111–23.

[14] Landis RJ, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;**33:**159–74.

[15] Wanner A. Allergic mucociliary dysfunction. *J Allergy Clin Immunol* 1983;**72:**347–50.

[16] Wasserman SJ. Ciliary function and disease. *J Allergy Clin Immunol* 1984;**73:**17–19.

[17] Mezey RJ, Cohn MA, Fernandez EJ, Januskiewicz AJ, Wanner A. Mucociliary transport in allergic patients with antigen-induced bronchospasm. *Am Rev Respir Dis* 1978;**118:**677–84.

[18] Wihl JA, Mygind N. Studies on the allergen-challenged human nasal mucosa. *Acta Otolaryngol* 1977;**84:**281–6.

[19] Dulfano MJ, Luk CK. Sputum and ciliary inhibition in asthma. *Thorax* 1982;**37:**646–51.

[20] Shelhamer JH, Marom Z, Kaliner M. Immunologic and

neuropharmacologic stimulation of mucous glycoprotein release from human airways in vitro. *J Clin Invest* 1980;**66**:1400–8.

[21] Yamatake Y, Sasagawa S, Yanaura S, Kobayashi N. Allergy induced asthma with Ascaris suum administration to dogs. *Jpn J Pharmacol* 1977;**27**:285–93.

[22] Greenstone M, Cooper P, Warner J, Cole PJ. Effect of acute antigenic challenge on nasal ciliary beat frequency. *Eur J Respir Dis* 1983;**64**(suppl 128):449–50.

[23] Sakakura Y. Changes of mucociliary function during colds. *Eur J Respir Dis* 1983;**64**(suppl 128):348–54.

[24] Carson JL, Collier AM, Hu SS. Acquired ciliary defects in nasal epithelium of children with acute viral upper respiratory infections. *N Engl J Med* 1985;**312**:463–8.

[25] Wilson R, Alton E, Rutman A, *et al.* Upper respiratory tract viral infection and mucociliary clearance. *Eur J Respir Dis* 1987;**70**:272–9.

[26] Kaminski EJ, Fancher OE, Calandra JC. In vivo studies of the ciliastatic effects of tobacco smoke. Absorption of ciliastatic components by wet surfaces. *Arch Environ Health* 1968;**16**:188–93.

[27] Jeffery PK, Reid LM. The effect of tobacco smoke, with and without phenylmethyloxadiazole (PMO), on rat bronchial epithelium: a light and electron microscopic study. *J Pathol* 1981;**133**:341–59.

[28] Kollerstrom N, Lord PW, Whimster WF. A difference in composition of bronchial mucus between smokers and non-smokers. *Thorax* 1977;**32**:155–9.

[29] Stanley PJ, Wilson R, Greenstone MA, MacWilliam L, Cole PJ. Effect of cigarette smoking on nasal mucociliary clearance and ciliary beat frequency. *Thorax* 1986;**41**:519–23.

Correspondence and requests for reprints to Dr G M Corbo, Divisione di Pneumologia Pediatrica, Centio Auxologico Italiano, 28044 Verbania-Intra(No), Italy.

Accepted 11 October 1988

Archives of Disease in Childhood, 1989, **64,** 551–556

Management of oesophageal stenosis in epidermolysis bullosa dystrophica

I B KERN,* M EISENBERG,† AND S WILLIS*

**The Prince of Wales Children's Hospital, and †School of Biochemistry, University of New South Wales, Australia*

SUMMARY Seven patients with epidermolysis bullosa dystrophica and chronic and recurrent oesophageal lesions such as spasm, strictures, and complete occlusion were studied. Dysphagia could be cured with drugs if it was caused by bullae formation or spasm. If oesophageal strictures were present, endoscopy and bouginage with corticosteroid prophylaxis during the quiescent phase of the disease was a safe and useful procedure. We have also given corticosteroids, which reduced the oedema caused by bullae formation and oral phenytoin, which reduced epithelial detachment by inhibiting collagenase activity. Verapamil counteracted oesophageal spasm and pureed food during periods of dysphagia reduced blistering of the upper oesophagus.

Epidermolysis bullosa dystrophica is a group of hereditary mechanobullous disorders affecting both the skin and gastrointestinal mucosa (table). In the recessive type, trauma is followed by a separation of skin at the dermoepidermal junction and at the lamina propria of the mucous membrane, probably because of an increase in mutant collagenase activity.[1] The recessive type can be further subdivided into two forms, localised and generalised, on the electron microscopic appearance of the dermoepidermal junction in non-blistered skin. In the localised form there are recognisable anchoring fibrils below the basement membrane, but they are attenuated in appearance and sparse. In the generalised form (which is clinically more severe) the anchoring fibrils are absent.[2]

In the recessive type the bullous lesions of the skin are usually present at birth and they quickly spread to affect the skin and mouth. Healing is slow, with chronic scarring that leads to digital fusion (syndactyly) and flexion contractures of the fingers and toes. The mucosa of the mouth, pharynx, and oesophagus is often affected. Oesophageal problems develop insidiously and are caused by bullae formation, ulceration, and oedema, which ultimately lead to stricture formation that may in turn cause complete oesophageal obstruction with regurgitation of blood stained secretions.

In the dominant form of epidermolysis bullosa dystrophica the skin disease is milder, but patients may develop tight webs in the upper oesophagus. These develop several years later than in the recessive type.

In this paper we describe our experiences over a

Table *Ultrastructural abnormalities in epidermolysis bullosa dystrophica with oesophageal disease*

Disease	*Specific structural defect*	*Clinical signs*
Recessive epidermolysis bullosa dystrophica:	Separation below basal lamina	
Generalised	Absence of anchoring fibrils and collagenolysis	Oesophageal stricture always found
Localised	Variable decrease of anchoring fibrils and collagenolysis	Oesophageal stricture and webs often seen
Dominant epidermolysis bullosa dystrophica:	Separation below basal lamina	
Cockayne-Tauraine	Anchoring fibrils decreased and abnormal in skin that blisters easily	
Albopapular	Anchoring fibrils abnormal and decreased in all skin areas	Oesophageal webs

period of 17 years with the medical and surgical management of patients with epidermolysis bullosa dystrophica who also have serious oesophageal complications. We describe seven cases to illustrate the clinical course of the oesophageal lesions and the response to treatment. Six patients had the recessive type (four localised and two generalised), and one had the dominant type. Cineoesophagograms were carried out in all patients with particular attention to the posterior pharynx and upper oesophagus to avoid missing the oesophageal webs that indicate a more favourable prognosis. Radiological follow up studies provided new information with aetiological and therapeutic implications.

Case reports

LOCALISED RECESSIVE EPIDERMOLYSIS BULLOSA DYSTROPHICA

Case 1

A boy aged 17 was diagnosed as having the localised recessive type at birth. After the first week of life he had extensive oral ulceration requiring nasogastric feeding. At the age of 1 year he developed acute dysphagia, and a cineoesophagogram showed a thin web at the cricopharangeal level. Endoscopy with steroid prophylaxis was carried out with great difficulty because of microstomia and oral ulceration though the stricture was easily dilated to 20 G with Chevalier Jackson rubber bougies.[3] After seven months he again developed dysphagia and required further dilatation, which was performed in two stages. He was then given oral phenytoin, which he was still taking at the time of writing.

He required no further dilatations until the age of 11 when he developed acute obstruction secondary to impaction of food. Two similar episodes of acute obstruction occurred at the ages of 12 and 15 years, and both required oesophagoscopy and dilatation.

Case 2

A boy aged 14 was diagnosed as having the localised recessive type at 3 weeks of age; at the age of 10 months he was started on oral phenytoin. At the age of 2 years he had a haematemesis, and a barium swallow examination showed extensive mucosal ulceration in his mid oesophagus. His symptoms responded to a short course of steroids.

At the age of 6 he developed chronic dysphagia that worsened over a period of three months despite repeated courses of steroids. Barium studies showed a tight stricture in the mid oesophagus. He underwent dilatation to 27 G and was able to drink the same day. He required another dilatation two months later and remained free of symptoms for six years. At the age of 12 he again developed dysphagia and required two dilatations one week apart.

Case 3

A girl aged 8 had the localised recessive type diagnosed at the age of 4 months, and was started on oral phenytoin at the age of 2. At the age of 3 she presented with episodes of distressing nocturnal dysphagia that lasted about 90 minutes each and ended with a haematemesis. On admission her haemoglobin concentration was 60 g/l and she required transfusion. A cineradiograph showed a tight stenosis in the upper third of the oesophagus (fig 1). This was dilated to 22 G after treatment with prednisone. She required another dilatation three months later.

At 4 years of age she again developed recurrent dysphagia, usually at night, which was not relieved by a course of steroids. Radiographically she had a tight stricture of the mid oesophagus (fig 2). This was fully dilated to 28 G in two stages four months apart; although this relieved the dysphagia during the day it did little to reduce the frequency of the nocturnal episodes. It was thought on clinical grounds that these were partly the result of disturbed oesophageal motility and spasm precipitated by nocturnal gastro-oesophageal reflux, although reflux could not be shown by scintigraphy. The reported ability of calcium channel blockers to inhibit the contractions in normal human oesophagus and relieve the symptoms of nutcracker oesophagus prompted us to use oral verapamil in our patient, beginning with a single nightly dose of 40 mg; her nocturnal dysphagia ceased immediately, confirming that her symptoms were the result of oesophageal spasm. She had two further episodes of acute obstruction when she was 6 and 8 years old, both of which needed endoscopy and dilatation.

Case 4

A 9 year old girl had the localised recessive type diagnosed when she was 2 days old. At the age of 4 months she developed dysphagia when fed semisolid food. In the next seven months she had two episodes when she vomited casts of oesophageal mucosa. These were followed by prolonged complete dysphagia that responded to treatment with prednisone.

She remained asymptomatic until she was 6 years old, when her dysphagia recurred. Radiological examination of the oesophagus showed a mid oesophageal stricture and she was admitted to hospital for treatment with corticosteroids and oesophageal dilatation. She was drinking and eating a soft diet one day after operation.

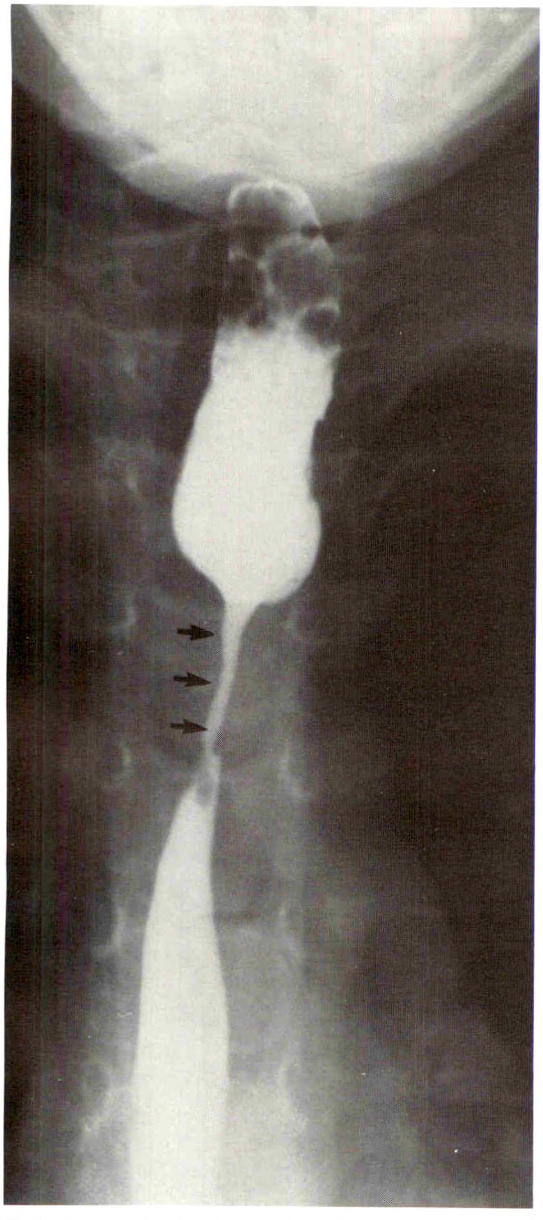


Fig 1 *Long stricture of cervical oesophagus in a 3 year old girl with severe dysphagia.*

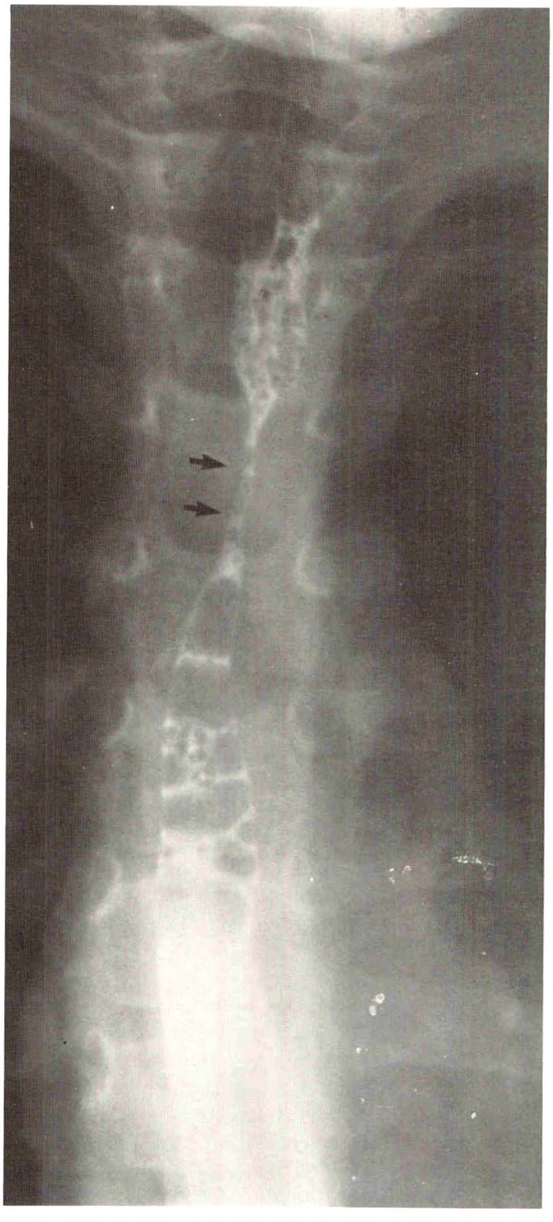


Fig 2 *Short stricture of mid oesophagus in a 4 year old patient with persistent bullous lesions of the oesophagus.*

GENERALISED RECESSIVE EPIDERMOLYSIS BULLOSA DYSTROPHICA

Case 5

A girl aged 4 years was first diagnosed as having the generalised recessive type at the age of 2½ years when she was first seen at this hospital. She spent 67 weeks in hospital during the first two years of life with recurrent skin infections, chest infections, chronic anaemia, and failure to thrive. At the age of 3½ years she had dysphagia, which was attributed to oropharangeal ulceration as barium studies had been reported as normal. One year later her dysphagia worsened so that she had to be maintained on a semiliquid diet. At the age of 4 years she was admitted to hospital because her general condition had deteriorated and there was radiological evidence of a tight oesophageal stricture just above the carina. Treatment with corticosteroids did not improve the dysphagia so oesophageal dilatation was carried out under general anaethesia. The stricture was dilated to 18 G without any difficulties. Postoperatively she initially made a good recovery, her condition was stable, and she drank a small amount of water. Five hours later she drank 300 ml of milk, and nine hours later suddenly collapsed, became pulseless, apnoeic, and died in spite of attempts at resuscitation. At necropsy a perforation of the lower oesophagus was found with a large amount of gastric contents within the peritoneal cavity, and her heart was enlarged.

Case 6

A boy aged 5 was diagnosed as having the generalised recessive type at birth. He was started on treatment with oral phenytoin at the age of 4 years 10 months. He had severe oral ulceration and tongue tethering that caused chronic dysphagia. He was investigated at this hospital at the age of 4, and a subcricopharyngeal web was diagnosed on oesophagogram. Six months later his dysphagia increased for two weeks. A tight, long stricture in the upper oesophagus was dilated with difficulty to 20 G. After the experience with case 5 distal oesophagoscopy was not attempted. The stricture was electively dilated again six weeks later to 27 G.

DOMINANT EPIDERMOLYSIS BULLOSA DYSTROPHICA

Case 7

A girl aged 14 was born with bullous lesions affecting all four limbs but the dominant form of the disease was only diagnosed at the age of 18 months. From the age of 8 years she had dysphagia caused by solid food that increased over the next two years until she could only swallow pureed food. At the age of 10 years she had an episode of aspiration pneumonia. Radiological examination of the oesophagus showed a cricopharyngeal web.

At the age of 11 she had an acute obstruction at the level of C6 by a bolus of meat, which passed spontaneously. Because of these complications she was admitted to hospital for oesophageal dilatation. This was accomplished without difficulties but had to be repeated three times in the next three years.

Discussion

Oesophageal disease in recessive epidermolysis bullosa dystrophica is the most serious complication after the first year of life. Barium studies of the oesophagus in the early stages show non-specific inflammatory changes—mucosal oedema, superficial ulceration, and areas of inconstant spasm.[4] As diffuse inflammatory changes progress to scarring, motility disturbances become more pronounced. Oesophageal trauma leads to stricture formation, which occurs most commonly in the upper third (50%) followed by the lower third (25%). Once strictures have formed they are permanent, and the patients are at risk of developing complete occlusion of the lumen of the oesophagus by a food bolus trapped at the site of the stricture. Oesophageal stenosis and obstruction may therefore eventually become the central problem for these patients, and lead to severe malnutrition, refractory anaemia, and (as in case 5) to aspiration pneumonitis.

In all our patients, when there were symptoms of severe obstruction, we often found it difficult to know whether the obstruction was caused by bullae, spasm, or stricture; radiological examination during the acute period did not always help to differentiate between them. Treatment at this stage was therefore symptomatic and aimed at decreasing the formation of oesophageal bullae and preventing aspiration of food and secretions. All our patients with the recessive type had moderate to severe malnutrition and case 3 had profound anaemia as a result of blood loss. High doses of corticosteroids (prednisone 2·5 mg/kg or the equivalent given intravenously as hydrocortisone) were effective in decreasing dysphagia, usually within 48 hours. Doses of steroids were gradually reduced over a two week period after the symptoms had subsided. Oesophageal dilatation was undertaken when the dysphagia failed to respond to medical treatment. In all our patients with chronic dysphagia, dilatation was carried out only when the skin disease was sufficiently quiescent.

We have performed 23 oesophageal dilatations in seven patients with epidermolysis bullosa dystrophica. Four were for acute obstructive symptoms (case 1), which required immediate intervention, and 19 were for increasingly incapacitating dysphagia caused by stricture formation. All the patients with the recessive type were taking phenytoin, which was maintained at a plasma concentration of 10 μg/ml. Clearly the drug has proved to be effective in the treatment of the skin lesions,[5–7] and it seems to be most beneficial in young patients at the time of the onset of their oesophageal symptoms. It was clear from our results that phenytoin was less effective when given at the time of dilatation of strictures.

The dilatations were performed through a rigid oesophagoscope using Chevalier Jackson rubber tipped dilators. The general anaesthetic technique has been described previously.[8 9] Induction was by inhalation, either by mask or head box, and the endotracheal tube was held in place throughout the whole procedure. There were no tracheal problems postoperatively. The death of case 5 resulted from a cardiac arrest due to rupture of the weakened oesophagus. The incidence of perforation of the oesophagus during endoscopy is low, and this usually manifests itself by shock, dyspnoea, and chest or abdominal pain. The management is operative and usually successful.[10] In this patient the cardiac arrest was caused by the added shock of peritonitis on a diseased mycardium. After this we modified our technique in patients with generalised disease, and only dilated the stricture, making no attempt to visualise the distal oesophagus. With the exception of that case there were no other complications. All patients were on full oral feeding by the next morning and were fit for discharge that day. Postoperatively as much normal solid diet as could be tolerated was encouraged to help maintain the dilatation.

One child experienced episodes of oesophageal spasm that were precipitated by gastro-oesophageal reflux and that responded immediately to oral verapamil.[11] This drug, a calcium channel blocker, is a potent inhibitor of oesophageal spasm and has brought relief to this patient for the past two years.

The natural history of oesophageal disease in our patients was stricture formation beginning at about the age of 2 years that required several dilatations over a period of months, followed by a few years of quiescence that was possibly due to treatment with phenytoin. Disturbances of oesophageal motility occurred in all patients, but in case 4 they were a serious problem and successfully managed with verapamil. This is the first report that we know of the use of this drug in the treatment of epidermolysis bullosa dystrophica.

A review of published reports shows that some authors were reluctant to recommend endoscopy and bouginage because of fear that tangental shearing forces could cause further mucosal damage.[12] Feurle *et al* report the use of inflatable dilator balloons that produce vertical pressure that seems to be less traumatic.[13] The difficulty of using this technique in children is the need for the patient to swallow a bead fixed to a string that serves as a guide for the balloon. It may, however, be necessary to use a balloon dilator introduced over a guide wire to keep the area of stricture open once it has been dilated at endoscopy.[14]

Colonic interposition has been carried out in a limited number of patients for whom eating had become a serious problem.[15] Harmel used a reversed gastric tube constructed from the greater curvature of the stomach in one patient.[16] These operations should be reserved for patients with extensive mucosal lesions or those in whom dilatation has caused mucosal injury and aggravated the dysphagia. Although colonic interposition has been used successfully to relieve dysphagia in these patients it is an operation with considerable morbidity—for example, anastomotic leaks and strictures that require further dilatation and cause inconvenience by lengthening the hospital stay. There is also a risk of cancer in the bypassed oesophagus that cannot be seen either radiologically or endoscopically.

The aim of this paper was to report our experience with the medical management of oesophageal lesions in patients with epidermolysis bullosa dystrophica. Treatment in the acute stage was aimed at decreasing bullae formation by treatment with high doses of prednisone. Motility disturbances were effectively managed with verapamil. Our report clearly showed that dilatation of acute and chronic strictures was successful and rewarding for our patients with incapacitating dysphagia. We feel that this procedure has an important role in the management of such children, and compares favourably with colonic interposition.

References

[1] Bauer EA. Recessive dystrophic epidermolysis bullosa: evidence of an altered collagenase in fibroblast cultures. *Proc Natl Acad Sci USA* 1977;**74**:4646–50.

[2] Eady RAJ. Diagnosing epidermolysis bullosa. *Br J Dermatol* 1983;**108**:621–6.

[3] Katz J, Gryboski J, Rosenbaum HM. Dysphagia in children with epidermolysis bullosa. *Gastroenterology* 1967;**52**:259–62.

[4] Agha FP, Francis IR, Ellis CN. Esophageal involvement in epidermolysis bullosa dystrophica: clinical and roentgenographic manifestations. *Gastrointest Radiol* 1983;**8**:111–7.

[5] Eisenberg M, Stevens LH, Schofield PJ. Epidermolysis bullosa-new therapeutic approaches. *Australas J Dermatol* 1978;**19**:1–8.

[6] Bauer EA, Cooper TW, Tucker DR, Esterly NB. Phenytoin therapy of recessive dystrophic epidermolysis bullosa. *N Engl J Med* 1980;**303**:776–81.

[7] Bauer EA, Cooper TW. Therapeutic considerations in recessive dystrophic epidermolysis bullosa. *Arch Dermatol* 1981;**117**:529–30.

[8] Fisk GC, Kern IB. Anaesthesia for oesophagoscopy in a child with epidermolysis bullosa—a case report. *Anaesth Intensive Care* 1973;**1**:297–300.

[9] Boughton R, Crawford MR, Vonwiller JB. Epidermolysis bullosa-15 years' experience. *Anaesth Intensive Care* 1988 (in press).

[10] Eadmark T, Sandberg N, Pettersson G. Instrumental perforation of the oesophagus—a ten year study from two ENT clinics. *J Laryngol Otol* 1986;**100**:461–5.

[11] Becker BS, Burakoff R. The effect of verapamil on the lower esophageal sphincter pressure in normal subjects and in achalasia. *Gastroenterology* 1983;**78**:773–5.

[12] Orlando RC, Bozymski EM, Briggaman RA, *et al*. Epidermoly-

Archives of Disease in Childhood, 1989, **64**, 557–562

Minor congenital anomalies and ataxic cerebral palsy

G MILLER

Neuromuscular Research Institute of Western Australia

SUMMARY The incidence of minor congenital anomalies was examined in 36 patients with ataxic cerebral palsy, in unaffected family members, and in 100 unrelated control subjects. None of the control subjects or family members had more than four anomalies, and 25 of 36 (69%) of the patients had more than four. The distribution of anomalies differed considerably, with 60% of the index cases having seven or more, and 94% of the controls having three or less. The number occurring in the patients was significantly more than in their relatives. Of the 25 patients with more than four anomalies, 16 (64%) had undergone potentially adverse perinatal or early postnatal events. Thus minor congenital anomalies were considerably more frequent in those with ataxic cerebral palsy than in related or unrelated control subjects. These anomalies may be markers of early prenatal factors that contributed to the adverse outcome either directly or by predisposing to perinatal difficulties.

Retrospective allocation of a cause of cerebral palsy is strongly influenced by observer bias. It has often been guessed at after reading inadequately recorded histories, and coloured by known associations such as preterm birth and diplegia.[1] It would therefore be of value to devise some marker that might indicate an association with a prenatal event, such as minor congenital anomalies. These are relatively infrequent physical features that in themselves have neither medical nor cosmetic importance.[2] They are harmless phenomena that may occur in completely healthy individuals. The recognition of these indicators of altered morphogenesis does, however, alert the clinician to the possibility of a more serious defect, and it has been argued that in excess they correlate with disturbances of neurological development occurring during embryogenesis.[3-6] In ataxic cerebral palsy these early prenatal disturbances are probably of the utmost importance.[7] Patients with this syndrome were therefore examined to find out whether they had significantly more minor congenital anomalies than a normal population and their own families. The prenatal, perinatal, and postnatal histories were also analysed.

The purpose of this study was to see if patients with ataxic cerebral palsy had more minor congenital anomalies, and if so to see if this finding correlated with the history.

Patients and methods

DIAGNOSIS

Cerebral palsy is defined as a group of disorders of movement and posture due to a non-progressive defect or lesion of the developing brain.[8] When this disorder is an ataxia that is not primarily due to muscle weakness, spasticity, choreoathetosis, or dystonia, it is called ataxic cerebral palsy. Thirty six cases, all over 5 years of age, were found, and personally examined to ensure that they fulfilled the criteria for diagnosis.

HISTORY

A full history was taken. Further information and as many aspects as possible were checked against the records of various institutions, hospitals, medical practitioners, and a comprehensive cerebral palsy register.[9] Particular emphasis was placed on certain aspects.

Prenatal history

This included items such as drugs, maternal illnesses and accidents, surgical operations, threatened abortions and antepartum haemorrhage, toxaemia, length of gestation, and birth weight. Events that occurred after 4 months' gestation and before the onset of labour were termed late prenatal. Where there was an uneventful history, evidence of Mendelian inheritance, or the presence of overt congenital abnormalities, then an association with the period of embryogenesis was implied. These findings were termed early prenatal.

Perinatal history

This covered the time from the onset of labour up until day 7 of life. It included quality and quantity of labour, presentation, obstetric intervention, measures of fetal distress, resuscitation, time to spontaneous respiration, Apgar scores, and condition during the first week of life—for example, tube feeding, assisted ventilation, seizures, intracranial haemorrhage, and infection of the central nervous system.

Postnatal history
This covered the time from day 7 to 2 years of age. Events sought included severe illnesses (particularly if they concerned the central nervous system) and serious surgical operations.

MINOR CONGENITAL ANOMALIES
The index cases, their parents and siblings, any children of the siblings, and a control group were examined for the presence of minor congenital anomalies. The control subjects (100) consisted of adults and children over 5 years of age in whom there was no history of neurodevelopmental disability. They were chosen at random from those attending a busy primary care clinic. All the subjects were caucasian.

The minor congenital anomalies studied were selected if they were either indisputably recognisable or easily measured. They were all characteristics determined by about the 16th week of gestation. The methods for indentification, measurement and normal values have been well described previously.[10–13] Forty four anomalies were sought (table 1). The aim was to see if the index cases had more anomalies than their families or a control population. If there was a significant difference this was taken to indicate an association with an event during embryogenesis (that is, early prenatal) and compared with the patient's history.

Results

Thirty six patients (two of whom were sisters) were diagnosed as having ataxic cerebral palsy; their mean age was 14 years (range 5–34).

Table 2 shows the incidence of minor congenital anomalies in the control population; none had more than four. Thus if more than four were found in any of the cerebral palsy patients, this was considered significant. The probability of misclassifying a control as a patient using this discriminant is statistically highly unlikely (binomial distribution, $p<0{\cdot}0005$).

Table 3 shows the number of minor congenital anomalies in the index cases and the family members. For the analysis, the sign test was carried out by examining the difference between the number of anomalies in the patient and the number in the relative with the maximum number of minor congenital anomalies; the patients had significantly more ($p<0{\cdot}01$). Apart from the family with two affected sisters, no family member had more than four minor congenital anomalies.

The relevant parts of the histories (some of which contained events that might retrospectively have been thought to contribute towards the neurological deficit) and the number of minor congenital anomalies found are given in tables 4 and 5. Table 4 shows those cases in which an early prenatal event might be associated with the devélopment of cerebral palsy as judged from their histories, and table 5, those

Table 1 *Minor congenital anomalies*

Mouth:
- High arched palate
- Furrowed tongue
- Bifid uvula

Hair:
- Two or more parietal whorls
- Abnormal posterior whorl
- Cowlick
- Widow's peak

Hands:
- Clinodactyly
- Partial cutaneous syndactyly
- Simian crease
- Sydney crease
- Middle finger/hand size
- Hypoplastic nails

Trunk:
- Accessory nipples

Feet:
- Broad hallux
- Hypoplastic hallux
- Wide distance between first and second toes
- Third toe longer than second
- Deep crease between first and second toes
- Syndactyly
- Overriding or curly toes

Eyes:
- Epicanthic folds
- Upslanting of palpebral fissures
- Downslanting of palpebral fissures
- Hypertelorism
- Hypotelorism

Ears and neck:
- Malformed ears
- Asymmetric ears
- Preauricular tags
- Preauricular pits
- Protruding ears
- Adherent ear lobes
- Lack of lobulus
- Incomplete scapha helix
- Neck webbing
- Small ears
- Low set ears
- Abnormally slanted ears
- Ear lobe creases

Face and nose:
- Synophrys (under 10 years)
- Coarse prominent supraorbital ridges
- Prominent metopic suture
- Anteverted nostrils
- Bifid tip of nose

Table 2 *Incidence of minor congenital anomalies in control population (n=100)*

No of anomalies/person	*Percentage of control population*
0	17
1	34
2	28
3	15
4	6

Table 3 *Minor congenital anomalies in patients and family members*

Case No	*No of anomalies/ patient*	*No of anomalies among family members**
1	7	2, 1, 1, 1
2	4	3, 2, 2, 2
3	6	3, 2, 2, 1
4	2	1, 0, 1, 2
5	7	2, 2, 0, 1
6	4	2, 4, 1, 2
7	7	1, 3, 1, 2
8	6	0, 0, 1, 1
9	9	1, 2, 2, 1, 2
10	9	2, 2, 0, 1
11	8	1, 2, 1, 2
12	1	1, 0, 2, 2, 2
13	2	1, 2, 1, 0
14	3	4, 1, 1, 1
15	8	3, 3, 3, 1
16	9	2, 2, 0, 4, 3
17	1	1, 0, 3, 1, 4
18	7	1, 1, 2, 1
19	5	1, 1, 1, 0
20	6	1, 1, 2, 1
21	2	3, 3, 2, 0
22	3	2, 3, 0, 2
23	7	3, 2, 1, 3
24	4	1, 1, 1, 0
25	6	0, 1, 1, 2, 1
26	8	0, 0, 1, 1
27	6	1, 0, 1, 1
28	6	0, 2, 2, 1
29	10	1, 0, 1, 0
30	9	2, 2, 0, 1, 3
31	6	1, 0, 2, 2, 2
32	6	1, 0, 2, 2, 2
33	6	0, 1, 1, 1
34	8	0, 3, 3, 1
35	0	2, 1, 1, 0
36	7	1, 3, 3, 2

*The family member with the greatest number of anomalies was used for comparsion.

Table 4 *Patients in whom early prenatal events were thought to have been associated with cerebral palsy*

Case No	*No of minor congenital anomalies*	*History*
1	7	Uneventful
15	8	Uneventful
16	9	Uneventful
18	9	Threatened abortion
20	6	Uneventful
29	10	Uneventful
30	9	Uneventful
31	6	Sister with similar condition, possible Joubert's syndrome
32	6	As case 31
33	6	Encephalocele
36	7	Uneventful
4	2	Mother has similar non-progressive condition
22	3	Congenital hydrocephalus, frequent blocked shunts
24	4	Uneventful
35	0	Suprasellar cyst. Several episodes of decompensated hydrocephalus

with a possible late prenatal, perinatal, or postnatal association. Unless otherwise stated, all were of normal birth weight and gestation.

When using the presence of more than four minor congenital anomalies to imply an early prenatal origin, 25 of 36 (69%) cases were found. Most of these obviously differed from the controls, 15 of them (60%) having seven or more anomalies.

Of the 15 cases (table 4) with a history suggesting an early prenatal cause, 11 (73%) had more than four minor congenital anomalies. When the numbers of patients with histories suggesting an association with early prenatal events are combined with those with more than four minor congenital anomalies, the total becomes 29 of 36 (81%). There are four cases (4, 22, 24, 35) shown in table 4 who did not have more than four minor congenital anomalies but whose histories suggested an early prenatal origin. Case 4 had a mother with a similar non-progressive condition, cases 22 and 35 had congenital hydrocephalus with histories of frequent episodes of raised intracranial pressure (which could be responsible for the ataxic syndrome), and case 24 had four minor congenital anomalies and none of his family had more than one.

There are three cases (3, 12, 13) which, from their histories, seem to be of postnatal origin; two of these did not have more than four minor congenital anomalies. The third case was a 'near miss SIDS' and one might speculate that the infant was abnormal before the event.

Of the 25 cases with more than four minor congenital anomalies, 16 (64%) had serious obstetric complications. Eight had abnormal presentations, five of whom had failed attempted versions, several required resuscitation at birth, were slow to establish spontaneous respirations, or were documented as having fetal distress.

Discussion

Since the description by Little in 1862 of the influence of prematurity and abnormal birth on the development of child handicap,[14] many clinicians and non-medical personnel have easily attributed the cause of cerebral palsy to these events. This is despite the statement by Freud as long ago as 1897 that it is impossible to identify the timing or nature

Table 5 *Patients in whom events occurring after four months' gestation were thought to be associated with cerebral palsy*

Case No	*No of minor congenital anomalies*	*Suggested pathogenetic period from history*	*History*
5	7	Perinatal	Thirty five weeks preterm, instrumental breech delivery, resuscitation required at birth
7	7	Perinatal	Delay in second stage, fetal distress, delivery by forceps under general anaesthesia
8	6	Late prenatal	Severe pre-eclamptic toxaemia
9	9	Perinatal	Occipitoposterior presentation, delay in second stage, fetal distress with meconium stained liquor
10	9	Perinatal	Prolonged second stage, more than three minutes to establish spontaneous respiration, resuscitation after birth
11	8	Perinatal	Occipitoposterior presentation, vacuum extraction, resuscitation after birth
19	5	Perinatal	Threatened abortion, failed external version twice at seven months, followed by version under general anaesthesia, placental separation and large antepartum haemorrhage
23	7	Perinatal	Apgar score of 5 at five minutes, more than three minutes to establish spontaneous respirations
25	6	Late prenatal and perinatal	Threatened abortion, antepartum haemorrhage at five months, eclamptic seizures, 33 weeks preterm, high forceps delivery, resuscitation after birth
26	8	Late prenatal and perinatal	Threatened abortion twice, failed external version, deep transverse arrest, rotation with Kielland's forceps under caudal block
27	6	Late prenatal and perinatal	External version three times, second stage less than five minutes, more than three minutes to establish spontaneous respirations
28	6	Late prenatal and perinatal	External version twice, fetal distress, delay in establishing spontaneous respirations, resuscitation required after birth
34	8	Perinatal	Preterm twin
2	4	Late prenatal	Severe pre-eclamptic toxaemia, SGA
6	4	Perinatal	Vacuum extraction for fetal distress
14	3	Perinatal	Twenty eight weeks preterm, resuscitation required at birth, necrotising enterocolitis requiring operation at 6 days
17	1	Perinatal	Twin, transverse lie, breech delivery, neonatal brain abscess, hydrocephalus, frequent blocked shunts
21	2	Perinatal	Fetal distress, emergency caesarean section, over two minutes to establish spontaneous respirations
3	6	Postnatal	'Near miss SIDS'
12	1	Postnatal	Encephalitis at 2 years of age
13	2	Postnatal	Severe shock and 'collapse' after operation for reimplantation of ureters at 3 months

of the event that caused the brain damage, and that there may be many factors operating in the prenatal, perinatal, and postnatal periods.[15] He proposed that some cases were caused by both predisposing and immediate events, and later authors have given this some support.[16-18] Paneth wrote that the hypothesis of a direct association between parturitional difficulties and cerebral palsy influences the practices of many obstetricians and paediatricians, and accounts in part for high rates of malpractice.[18] Epidemiological studies, however, have not supported this hypothesis.[17] It seems that most cerebral palsy is of early prenatal origin, or has a prenatal event that makes an important contribution to its aetiology. Severe asphyxial intrapartum and perinatal events may, however, be associated with later neurological deficit if the baby survives,[19 20] even though many of these survivors may be intact. This has led to increasing obstetric awareness, monitoring, and intervention, even though little correlation has been found between markers of fetal distress and later disability (MJ Painter, M Scott, R Depp. Neurological and developmental follow up of children at 6 to 9 years relative to intrapartum fetal heart rate patterns. Presented at the Society of Perinatal Obstetricians annual meeting, Las Vegas, 1985),[21] and the incidence of cerebral palsy is not falling.[22] Despite these statements it is difficult for those concerned in the care of handicapped children not to attribute a primarily causative role to serious obstetric complications.

This study evaluated these factors by finding out that in a select cerebral palsy population, a high proportion of which were expected to be of early prenatal origin, most had more than four minor congenital anomalies. These characteristics would have been determined by about 16 weeks' gestation, or earlier. The distribution of anomalies in the controls and the index cases differed considerably, with 60% of the index cases having seven or more minor congenital anomalies, and 94% of the controls three or less. The method would have benefited from an interobserver control. The minor congenital anomalies chosen were, however, indisputably present, or easily measured and compared with established normal values. The incidence of minor congenital anomalies, and what constitutes a significantly increased number, vary among studies, probably because different methods have been used and different features have been sought, the incidence increasing with the number.[23] The results of many studies have suggested that excessive numbers of minor congenital anomalies correlate with disturbances of neurological and mental development,[3–6,24] and this study supports this view. Although the association is difficult to prove,[25] a significantly increased number of minor congenital anomalies in a patient with a static encephalopathy provides strong circumstantial evidence of an early prenatal contribution to the disorder. This study is not claiming a definite causal relationship, however, but is reporting an association.

It would seem then that a controlled search for a significantly increased number of minor congenital anomalies in a cerebral palsy population might supply circumstantial evidence for a pathogenetic period. Using this method, this study shows the importance of an association between early prenatal and later events. Of those with an increased number of minor congenital anomalies, 64% had later adverse events, many of which might have been thought to be primarily causal. A recent study of congenital anomalies in high risk children also reported this association,[26] although they excluded the most severely handicapped children, and their obstetric complications were not as serious as those presented here. The National Collaborative Perinatal Project has reported the poor correlation between 'obstetric risk factors' and cerebral palsy, and has shown an association between markers of asphyxia and major congenital malformations or other intrinsic defects that might have contributed to an unfavourable outcome.[17] One of the predictors of cerebral palsy was breech presentation and in this present study eight had abnormal presentations, five of which had failed attempts at external version and fetal distress.

The historical data given are retrospective, and at times their recording was somewhat variable, although obtained from multiple sources. They are presented to show that even the most unfavourable recorded perinatal events, that are followed by cerebral palsy, may be associated with evidence of an earlier prenatal insult. The results suggest that if further prospective studies were carried out on larger populations using the methods described here, added support would be given to the concept that although adverse perinatal events have the potential to cause brain injury, and interfere with subsequent development, their role in producing later neurological impairment should not be overestimated.

I am indebted to Dr Fiona Stanley and Ms Linda Watson for access to the cerebral palsy register of Western Australia, to Dr Valerie Gracey for statistical advice, and to those with cerebral palsy and their families who participated in the study.

References

[1] Stanley FJ. Prenatal risk factors in the study of the cerebral palsies. In: Stanley FJ, Alberman E, eds. *The epidemiology of cerebral palsies.* Clinics in Developmental Medicine No 87. Oxford: Blackwell, 1984:87–97.

[2] Marden PW, Smith DW, McDonald MJ. Congenital anomalies in the newborn infant: including minor variations. *J Pediatr* 1964;**64:**357–71.

[3] Hook EB, Marden PM, Reiss NP, Smith DW. Some aspects of the epidemiology of human minor birth defects and morphological variants in a completely ascertained newborn population (Madison Study). *Teratology* 1976;**13:**47–56.

[4] Smith DW, Bostian KE. Congenital anomalies associated with idiopathic mental retardation. *J Pediatr* 1964;**65:**189–96.

[5] Neuhauser G, Vogt J. Minor craniofacial anomalies in children. *Eur J Pediatr* 1980;**9:**243–50.

[6] Arima M, Komiyak K, Ono K, Hisada K. Congenital minor anomalies in mentally retarded children. *Proceedings of the Australian Association of Neurologists* 1968;**5:**177–82.

[7] Sanner G, Hagberg B. 188 cases of non-progressive ataxic syndromes in childhood. *Neuropediatrics* 1974;**5:**224–35.

[8] Bax M. Terminology and classification of cerebral palsy. *Dev Med Child Neurol* 1964;**6:**295–7.

[9] Stanley FJ. An epidemiological study of cerebral palsy in Western Australia, 1956–1975. 1: Changes in total incidence of cerebral palsy and associated factors. *Dev Med Child Neurol* 1979;**21:**701–13.

[10] Méhes K. *Minor malformations in the neonate.* Budapest: Akadémiai Kiadó, 1983.

[11] Joseph M, Dawbarn C. *Measurement of the facies. A study in Down's syndrome.* SIMP Research Monograph No 3. London: Heinemann, 1970.

[12] Feingold M, Bossert WH. Normal values for selected physical parameters: an aid to syndrome delineation. *Birth Defects* 1974;**X:**1–16.

[13] Smith DW. Origin and relevance of aberrant scalp and upper facial hair patterning. *Birth Defects* 1975;**XI:**207–12.

[14] Little WJ. On the influence of abnormal parturition, difficult labour, premature birth, and asphyxia neonatorum on the mental and physical conditions of the child, especially in relation to deformities. *Transactions of the Obstetrical Society of London* 1862;**3:**293–344.

[15] Freud S. *Infantile cerebral paralysis (1897).* Translated by Russin LA. Florida: University of Miami Press, 1967:137.

[16] Task force on joint assessment of prenatal and perinatal factors associated with brain disorders. National Institutes of Health report on cause of mental retardation and cerebral palsy. *Pediatrics* 1985;**76:**457–8.

[17] Nelson KB, Ellenberg JH. Antecedents of cerebral palsy. Multivariate analysis of risk. *N Engl J Med* 1986;**315:**81–6.

[18] Paneth N. Birth and the origins of cerebral palsy. *N Eng J Med* 1986;**315:**124–6.

[19] Myers RE, Adamson K. Obstetric considerations of perinatal brain injury. In: Scarpelli EM, Cosmi EV, eds. *Reviews in perinatal medicine*. New York: Raven Press, 1981:221–48.

[20] Ishikawa T, Ogawa Y, Kanayama M, Wada Y. Long term prognosis of asphyxiated full-term neonates with CNS complications. *Brain Dev* 1987;**9:**48–53.

[21] Crane J, Anderson B, Marshall R, Harvey P. Subsequent physical and mental development in infants with positive contraction stress tests. *J Reprod Med* 1981;**26:**113.

[22] Hensleigh PA, Fainstat T, Spencer R. Perinatal events and cerebral palsy. *Am J Obstet Gynecol* 1986;**154:**978–81.

[23] Leppig KA, Werler MM, Cann CI, Cook CA, Holmes LB. Predictive value of minor anomalies. 1. Association with major malformations. *J Pediatr* 1987;**110:**530–7.

[24] Kalbe U. Kleine Fehlbildungen bei Kindern mit Cerebralparese. *Der Kinderarzt* 1978;**9:**803–10.

[25] Holmes LB. Clinical indicators that time abnormal brain development. In: Freeman JM, ed. *Prenatal and perinatal factors associated with brain disorders*. Bethesda: National Institutes of Health, 1985:109–120. (NIH) 85–1149.

[26] Lindahl E, Michelsson K. Neurodevelopmental significance of minor and major congenital anomalies in high risk children. *Neuropediatrics* 1986;**17:**86–93.

Correspondence to Dr G Miller, Division of Pediatric Neurology, University Hospital, The Milton S Hershey Medical Center, PO Box 850, Hershey PA 17033, USA.

Accepted 1 December 1988

Archives of Disease in Childhood, 1989, **64,** 563–568

Prognostic value of creatine kinase BB-isoenzyme in high risk newborn infants

V J RUTH

Children's Hospital, University of Helsinki, Finland

SUMMARY Serum creatine kinase BB-isoenzyme (CK–BB) activity was studied on the first day of life in 31 acutely asphyxiated infants, 70 infants born after high risk pregnancies (pre-eclampsia or intrauterine growth retardation, or both), and 47 very low birthweight infants. Neurodevelopmental evaluation was carried out at 2·2–2·5 years. Eight infants died with, and eight without, hypoxic-ischaemic lesions of the brain, 14 had cerebral palsy, 16 had mild motor impairment, six had developmental delay without motor impairment, and 96 were normal at follow up. Infants who died with brain injury had significantly higher CK–BB activity than infants with normal outcomes (geometric mean 12 U/l); the mean difference was 82 U/l with a 95% confidence interval from 31 to 219 U/l. CK–BB in infants with cerebral palsy and mild motor impairment (geometric means 12 and 15 U/l, respectively) were similar to controls. CK–BB activity after birth is predictive of neonatal death but not of neurological damage in survivors.

Perinatal asphyxia is a common cause of neonatal mortality, and survivors are at risk of permanent brain damage, mainly cerebral palsy. In a population based study the incidence of cerebral palsy of perinatal origin was 1·1/1000 live births[1]; 47% of the handicapped infants had been born at full term. In low birthweight infants the incidence of brain injury was inversely correlated with gestational age with an overall incidence of 6·8% in survivors.[2]

The classical indicators of asphyxia (the Apgar score and cord pH) are poor predictors of brain damage,[3 4] so to detect a risk of hypoxic-ischaemic brain injury in the neonatal period more specific measurements are needed.

The BB-isoenzyme of creatine kinase (CK–BB) has been considered comparatively specific for brain tissue, and increased activity in serum[5] or cerebrospinal fluid[6] has been associated with brain damage in adults. Increased activity of CK–BB in serum has been reported in preterm infants with intraventricular haemorrhage,[7] and in asphyxiated infants born at full term.[8 9] Correlation between CK–BB activity and the neurological results of perinatal asphyxia has been reported, but the damaged survivors have been few.[10 11]

The aim of this follow up study was to find out if serum CK–BB activity on the first day of life is an indicator of perinatal brain damage.

Patients and methods

The infants studied were born in 1982–5 at the Women's Hospital, and, if necessary, treated at the neonatal intensive care unit of the Children's Hospital, University of Helsinki. The study protocol was approved by the ethical committees of both hospitals. Informed consent was obtained from both parents if possible.

Three groups of infants were studied. The acute asphyxia group infants (table 1) were born after uneventful pregnancy and spontaneous onset of labour, but had severe intrapartum asphyxia, defined as an Apgar score of 6 or less at 5 minutes (n=24) or an umbilical arterial pH of 7·05 or less (n=7). Two infants died of cerebral infarction at the ages of 1 and 8 days, and one died of asphyxia and septicaemia at the age of 14 hours.

The high risk pregnancy group (table 1) included nine infants with intrauterine growth retardation (less than two standard deviations below the mean) not associated with pre-eclampsia, and 61 infants born to mothers with severe pre-eclampsia. Forty eight fetuses had abnormal heart rate patterns before birth necessitating delivery by caesarean section in 40 cases. Fifty two infants were delivered between 25 and 36 weeks' gestation, and 31 infants needed intensive care. Seven infants died; two had

Table 1 *Clinical characteristics of subjects studied*

	Infants with acute asphyxia (n=31)	*High risk pregnancy (n=70)*	*Very low birthweight infants (n=47)*
Gestational age (weeks)*	39·4 (2·3)	34·0 (3·5)	29·0 (2·1)
Birth weight (g)*	3470 (770)	1830 (730)	1185 (210)
Small for gestational age	1	32	4
Male:female	13:18	39:31	23:24
Twin or triplet	2	6	17
Mode of delivery:			
Vaginal	14	16	21
Caesarean section	17	54	26
Umbilical arterial pH:			
Median (No of patients)	7·06 (16)	7·25 (50)	7·30 (4)
Range	6·57–7·29	7·12–7·39	7·27–7·33
Apgar score:			
At one minute 0–3	21	6	16
4–7	8	19	19
At five minutes 0–3	14	0	3
4–7	11	14	22
Neonatal diagnoses:			
Respiratory distress syndrome	1	14	27
Hypoxic-ischaemic encephalopathy:			
Mild	5	1	0
Moderate	8	0	0
Severe	6	0	0
Periventricular or intraventricular haemorrhage:			
Grade I	1	5	9
Grade II	0	1	4
Grade III	0	2	3
Grade IV	0	2	3
Mechanical ventilation >12 hours	19	22	37
Treatment with phenobarbitone	13	10	20
Death: neonatal/later	3/0	6/1	3/3

*Data expressed as mean (SD).

intracerebral haemorrhages and a third had infarction of the brain, but the other four infants had no signs of hypoxic-ischaemic brain damage at necropsy.

The very low birthweight group infants (less than 1500 g, table 1) were born after the acute onset of labour, or an acute maternal complication with no previous complications of pregnancy. All received intensive care for a median of 33 days. One infant died of renal tubular necrosis and intracerebral haemorrhage and one of tension pneumothorax and ischaemic brain lesions, but in the remaining four deaths no signs of hypoxic brain damage were found at necropsy.

Within each study group infants with adverse outcomes were compared with those with normal outcome. For ethical reasons no blood samples were taken from healthy control infants.

Blood samples were obtained at the age of 6–14 hours (median sampling age 10 hours). Serum was separated and stored at −20°C until analysis. Creatine kinase activity was measured using a Scandinavian standard method.[12] The proportion of activity due to the BB-isoenzyme was determined by an electrophoretic method on cellulose acetate, with a sensitivity of 2 U/l (Helena CPK Electrophoresis Procedure, Super CPK Isoenzyme Kit 5449).

Umbilical arterial blood pH was obtained from most of the asphyxiated and high risk pregnancy cases but only from four infants in the very low birthweight group. The Apgar score was routinely assigned at the age of 1 and 5 minutes by the attending paediatrician or midwife. Brain ultrasound examination was performed with a sector scanner (ATL, 5 or 7 MHz transducer) at least once during the first week and in preterm infants repeatedly during the first month.

Neurodevelopmental follow up was carried out by two paediatric neurologists unaware of the perinatal history. The methods have previously been reported in detail.[13 14] The end point for the present evaluation was an examination at 2·2–2·5 years of age, which included estimation of developmental quotient by a psychologist. The quotient was derived from the Bayley mental scale of infant development or the corresponding Terman-Merrill-Hellström test of mental and motor development,[14] and it was corrected for prematurity.

Based on these examinations the children were classified into four outcome categories: normal outcome, mild motor impairment (slight or transient abnormality in muscle tone or an abnormal pattern of motor development), cerebral palsy,[15] or developmental delay (mental developmental quotient less than 100, no motor dysfunction). Because neurodevelopmental delay without motor impairment can seldom be ascribed to perinatal asphyxia, perinatal brain damage was considered to be present in infants who died with hypoxic-ischaemic lesions of the brain and in infants who had cerebral palsy or mild motor impairment.

Data analyses were performed using the BMDP statistical software (BMDP Statistical Software Inc). Natural logarithmic transformation was done for CK–BB activities to correct for skewness of the distribution. The Mann-Whitney test, analysis of variance, and χ^2 tests were applied for comparison between the outcome categories as appropriate. Linear regression was used for analysing the associations between CK–BB activity and the measures of asphyxia, pH, and the Apgar score, as well as developmental quotient.

Results

The outcome of the infants in the three study groups is shown in table 2. Perinatal brain damage was present in a total of 38 infants: 16 had mild motor impairment, 14 cerebral palsy, and eight died of hypoxic-ischaemic lesions in the brain.

In the acute asphyxia group, CK–BB activity did not correlate with the Apgar score or with cord pH in the 16 infants who had this determined. CK–BB activities were similar in all three severity grades of hypoxic-ischaemic encephalopathy[16] and in those infants without it. No correlation was found between CK–BB activity and developmental quotient at 2 years. CK–BB activities in the infants with normal outcome and those with perinatal brain damage are shown in fig 1. The two infants with developmental delay without motor impairment (not included in the figure) had CK–BB activities below 2 U/l.

In the high risk pregnancy group, CK–BB did not correlate with the 5 minute Apgar score, cord pH, gestational age, or the degree of intrauterine growth retardation. Because CK–BB activities were similar in infants with grades I–III of intraventricular haemorrhage and in those without, the presence of

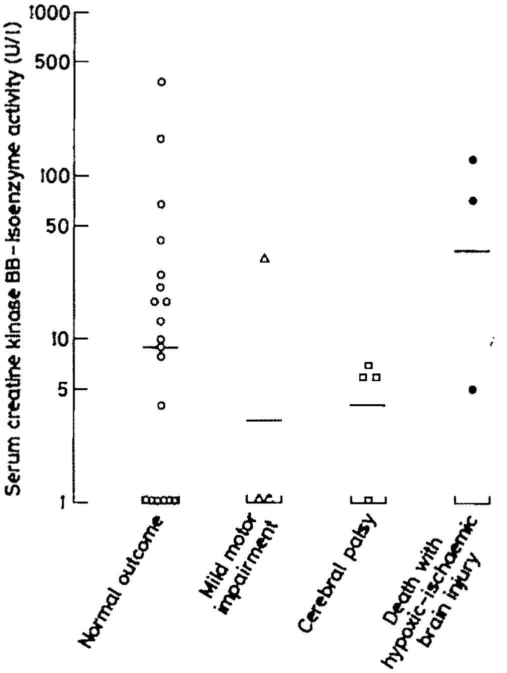


Fig 1 *Serum creatine kinase BB-isoenzyme activity in infants with acute birth asphyxia in relation to outcome at 2 years. Horizontal bars indicate the geometric mean of each category.*

Table 2 *Outcome of study subjects: deaths and results of neurodevelopmental follow up at 2·5 years*

	Infants with acute asphyxia	*High risk pregnancy*	*Very low birthweight infants*
Normal outcome	19	50	27
Mild motor impairment	3	7	6
Cerebral palsy, total	4	2	8
Diplegia	1	0	6
Tetraplegia	3	0	0
Hemiplegia	0	1	2
Dystonia	0	1	0
Developmental delay without motor impairment	2	4	0
Death with brain damage	3	3	2
Death without brain damage	0	4	4

haemorrhage was not a confounding factor when analysing CK–BB activity in relation to outcome. No correlation was found between CK–BB activity and developmental quotient. The infants who died with hypoxic-ischaemic brain lesions had significantly higher values (geometric mean 330 U/l) than those with normal outcomes (13 U/l), but infants with cerebral palsy or mild motor impairment did not differ from normal infants (fig 2); neither did the infants who died without hypoxic-ischaemic brain lesions (30 U/l) or those who had developmental delay without motor impairment.

In the very low birthweight group, no correlation was found between CK–BB activity, Apgar scores, or gestational age. The enzyme activities were similar in infants with all grades of intraventricular haemorrhage and in infants without. No correlation was found between CK–BB activity and the developmental quotient. The geometric means in infants with normal outcome, mild motor impairment, and cerebral palsy were 14, 29, and 20 U/l, respectively (fig 3). The two infants who died with brain damage had high values. The range of CK–BB activity in the four infants who died without brain injury was 7–31 U/l.

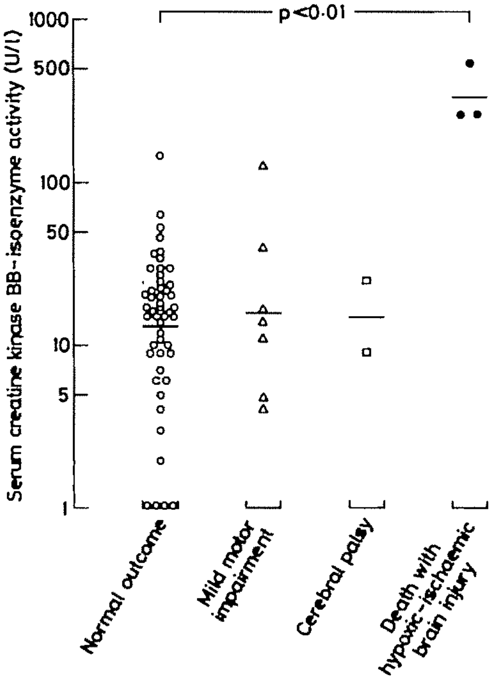


Fig 2 *Serum creatine kinase BB-isoenzyme activity in infants born after high risk pregnancy in relation to outcome at 2 years.*

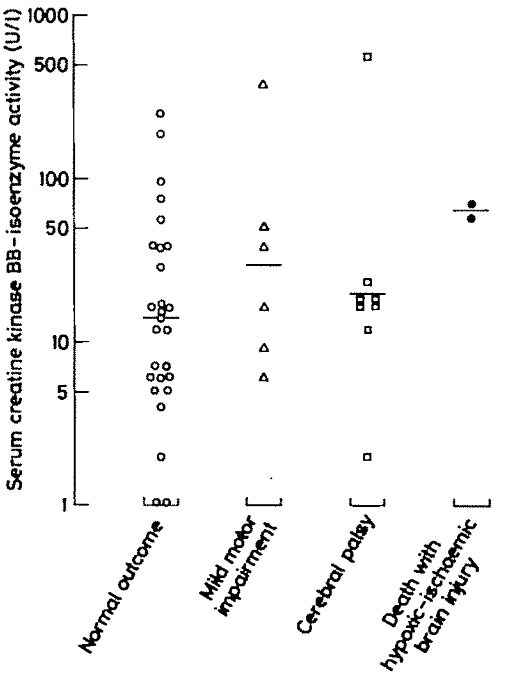


Fig 3 *Serum creatine kinase BB-isoenzyme activity in very low birthweight infants in relation to outcome at 2 years.*

CK–BB activities were similar in infants treated with phenobarbitone, which was given in most cases as part of a prophylactic trial,[14] and in those not receiving the drug (geometric means 16 and 13 U/l, respectively). When all three study groups were combined, infants who died with brain damage had significantly higher CK–BB activities than those with normal outcome (12 U/l), the mean difference was 82 U/l (95% confidence interval 31 to 219 U/l ($p<0·001$). The infants with mild motor impairment or cerebral palsy (geometric mean 15 and 12 U/l, respectively), however, did not differ from the normal ones.

Discussion

The method for determining CK–BB activity used in the present study has a sensitivity of 2 U/l, which is sufficient for the present purpose as CK–BB activity in healthy newborn infants is higher than in adults.[17] CK–BB activity in cord blood is about twice that in maternal blood,[9] and increases after birth with a peak at the age of about 5–10 hours.[10 11 17] The mode of delivery does not affect the CK–BB activity in cord blood or later during the first day.[17 18]

Although the main source of serum CK–BB in man is the brain, this isoenzyme is found in many tissues—for example, gastrointestinal tract, kidney, lung, liver, uterus, and placenta.[19] The vessel walls of both umbilical artery and vein have high CK–BB activities, even higher than placenta.[20] Thus cord blood CK–BB activity may be partly derived from uterine, placental, or umbilical tissues and cannot be considered specific for the fetal brain. Increasing activity in blood after birth, however, must be released from tissues in the newborn infant, and probably mainly the brain. This is suggested by the finding that infants with necrotising enterocolitis, or lung or kidney disease, do not have higher activities than control infants, whereas infants with severe asphyxia and neurological damage do.[9] In the present study the age at blood sampling (10 hours on average) was chosen on the basis of previous studies[10 17] close to the supposed peak activity.

In newborn infants who died of severe brain damage, serum CK–BB on day 1–4 was significantly increased.[8] By repeated serum CK–BB measurements, the outcome at a mean age of 7 months was predictable in 77% of 22 severely asphyxiated term infants.[10] In another study of 33 asphyxiated infants born at full term, adverse outcome could be predicted by CK–BB activity at the age of 4 hours.[11] Adverse outcome in both these studies, however, was usually death, as only three in the first and four in the second study survived with neurological abnormalities.

In the present study, severe brain damage leading to death in the neonatal period was associated with high CK–BB activities, especially after high risk pregnancy. Cerebral palsy or mild motor impairment, however, could not be predicted.

Brain injury in the young infant is not necessarily associated with the process of birth. Although most infants in the high risk pregnancy group had intrapartum asphyxia, the insult might have occurred earlier. In the other two groups damage during labour or at birth seems probable.

In cases with fatal intracerebral haemorrhage, CK–BB activity was high, whereas infants with grades I–III intraventricular haemorrhage had activities similar to those without bleeding. Significantly higher CK–BB activities on the first day have previously been found in infants with haemorrhage,[7] but the extent of the bleeding was more severe than in the present study.

It is likely that the release of CK–BB from damaged neurones and through the blood brain barrier is dependent on the severity of the insult. Enzyme activities in the cerebrospinal fluid of newborn infants could be a better predictor of brain damage than those in serum, as is the case in adults.[7] The aim of this study, however, was to look for a simple serum assay with the potential for screening infants at risk for brain damage, for which purpose a lumbar puncture would not be suitable. Unfortunately, serum CK–BB activity does not seem to be accurate enough.

In conclusion, a single measurement of CK–BB activity on the first day of life cannot be used as a prognostic indicator of long term neurological outcome, but high activities in critically ill newborn infants indicate a risk of neonatal death.

This study was supported by grants from the Foundation for Paediatric Research, the Sigrid Juselius Foundation, the Signe and Ane Gyllenberg Foundation, and Finska Läkaresällskapet. I thank Peter Elg for help with CK–BB determinations.

References

[1] Hagberg B, Hagberg G, Olow I. The changing panorama of cerebral palsy in Sweden. IV. Epidemiological trends 1959–78. *Acta Paediatr Scand* 1984;**73:**433–40.

[2] Powell TG, Pharoah PO, Cooke RI. Survival and morbidity in a geographically defined population of low birthweight infants. *Lancet* 1986;**i:**539–43.

[3] Nelson KB, Ellenberg JH. Apgar scores as predictors of chronic neurologic disability. *Pediatrics* 1981;**68:**36–44.

[4] Ruth VJ, Raivio KO. Perinatal brain damage: predictive value of metabolic acidosis and Apgar score. *Br Med J* 1988;**297:**24–7.

[5] Kaste M, Somer H, Konttinen A. Brain-typical creatine kinase isoenzyme. *Arch Neurol* 1977;**34:**142–4.

[6] Hans P, Born JD, Chapelle J-P, Milbouw G. Creatine kinase isoenzymes in severe head injury. *J Neurosurg* 1983;**58:**689–92.

[7] Shields WD, Feldman RC. Serum CK–BB isoenzyme in preterm infants with periventricular hemorrhage. *J Pediatr* 1982;**100:** 464–8.

[8] Becker M, Menzel K. Brain-typical creatine kinase in the serum of newborn infants with perinatal brain damage. *Acta Paediatr Scand* 1978;**67:**177–80.

[9] Cuestas RA. Creatine kinase isoenzymes in high-risk infants. *Pediatr Res* 1980;**14:**935–8.

[10] Walsh P, Jedeikin R, Ellis G, Primhak R, Makela SK. Assessment of neurologic outcome in asphyxiated term infants by use of serial CK–BB isoenzyme measurement. *J Pediatr* 1982;**101:**988–92.

[11] Fernandez F, Verdu A, Quero J, Perez-Higueras A. Serum CPK–BB isoenzyme in the assessment of brain damage in asphyctic term infants. *Acta Paediatr Scand* 1987;**76:**914–8.

[12] Hörder M, Magid E, Pitkänen E, *et al.* Recommended method for the determination of creatine kinase in blood modified by the inclusion of EDTA. *Scand J Clin Lab Invest* 1979;**39:**1–5.

[13] Ruth V, Autti-Rämö I, Granström M-L, Korkman M, Raivio KO. Prediction of perinatal brain damage by cord plasma vasopressin, erythropoietin, and hypoxanthine. *J Pediatr* 1988; **113:**885–5.

[14] Ruth V, Virkola K, Paetau R, Raivio KO. Early high-dose phenobarbital treatment for prevention of hypoxic-ischemic brain damage in very low birth weight infants. *J Pediatr* 1988;**112:**81–6.

[15] Hagberg B, Hagberg G, Olow I. The changing panorama of cerebral palsy in Sweden 1954–1970. II. Analysis of the various syndromes. *Acta Paediatr Scand* 1975;**64:**193–200.

[16] Fenichel GM. Hypoxic-ischemic encephalopathy in the newborn. *Arch Neurol* 1983;**40:**261–6.

[17] Jedeikin R, Makela S, Shennan AT, Rowe RD, Ellis G. Creatine kinase isoenzymes in serum from cord blood and the

blood of healthy full-term infants during the first three postnatal days. *Clin Chem* 1982;**28**:317–22.
[18] Ezitis J, Finnström O, Hedman G, Rabow L. CKBB-enzyme activity in serum in neonates born after vaginal delivery and cesarean section. *Neuropediatrics* 1987;**18**:146–8.
[19] Neumeier D. Tissue specific and subcellular distribution of creatine kinase isoenzymes. In: Lang H, ed. *Creatine kinase isoenzymes. Pathophysiology and clinical application.* Berlin: Springer Verlag, 1981: 85–115.
[20] Kumpel B, Wood SM, Anthony PP, Brimblecombe FS. Umbilical cord serum creatine kinase BB in the diagnosis of brain damage in the newborn: problems in interpretation. *Arch Dis Child* 1983;**58**:382–3.

Correspondence and requests for reprints to Dr V Ruth, Children's Hospital, Stenbäckinkatu 11, 00290 Helsinki, Finland.

Accepted 12 October 1988

Archives of Disease in Childhood, 1989, **64**, 569–572

Cranial ultrasound assessment of gestational age in low birthweight infants

N P MURPHY, J RENNIE, AND R W I COOKE

Neonatal Intensive Care Unit, Liverpool Maternity Hospital, Liverpool

SUMMARY The anatomical features of the cerebral hemispheres of 97 infants were studied by ultrasonography. A scoring system was devised based on anatomical and ultrasound appearances and compared with gestational age calculated from the date of the mother's last period. There was a significant positive correlation between gestational age and ultrasound score. Cranial ultrasonography is an accurate and reproducible method of assessing gestational age in low birthweight infants.

There is a need for accurate method of assessment of gestational age in very low birthweight infants. Preterm infants with appropriate birthweights for their gestational ages present problems of management that are different from those of infants who are small for gestational age.[1] Furthermore, the clinician requires an accurate baseline for follow up of growth and neurodevelopment. Existing methods of assessing gestational age are based on studies of infants of 32 weeks' gestation or more.[1] These methods are often inaccurate[2] or difficult to apply in the very low birthweight group.

Brain maturation based on necropsy appearances correlates well with gestational age according to the maternal menstrual history. From the 24th to the 34th week of gestation there are important identifiable changes in the cerebral surface,[3-5] and principal sulci develop and alter in complexity each week. After 34 weeks, as the gyri increase in complexity, distinctive changes are less easy to identify.[3]

Real time ultrasound is a non-invasive method of studying the important changes in the neonatal brain. This study was undertaken to assess the use of ultrasonography in determining gestational age in very low birthweight infants.

Patients and methods

All infants studied had been admitted to the neonatal intensive care unit and their scans were carried out during the first 3 days of life. The mean (SD) gestational age of the study group was 29·7 (2·5) weeks, range 24–34 weeks, and the mean (SD) birthweight was 1260 (420) g, range 610–2100 g. There were 55 boys and 43 girls. Gestational age was based on the mother's menstrual history.[6] Infants of mothers with irregular menstrual cycles or bleeding in early pregnancy were excluded. Also excluded were infants of mothers with prolonged rupture of membranes (longer than two weeks) or prolonged hypertension, or those who had been taking steroids for longer than two weeks, as these are associated with acceleration of neurological and pulmonary maturity in the fetus.[7] Note was also taken of each antenatal ultrasound assessment of gestational age[8] where these were in agreement with the mother's menstrual history and the fundal size.

Ultrasound scans were carried out through the anterior fontanelle using an ATL 850A sector scanner with 5 mHz transducers. Images were obtained in three planes, tangental, midsaggital, and coronal, and photographed with 'Polaroid' film to provide a permanent reproducible record.

The first appearance and increasing complexity of the principal sulci with increasing maturity in each place was noted (table). To standardise the assessment a scoring system was devised using diagrams based on anatomical and ultrasound appearances (fig 1).[3 4 5 7] The Polaroid prints were compared with the diagrams and scored by three independent observers skilled in the interpretation of neonatal cranial ultrasound scans but unaware of the clinical details of the patients.

Results

Ninety seven infants had ultrasound scans carried out during the first 3 days of life, and images in three planes (tangental, midsaggital and coronal) were produced on Polaroid prints of sufficient quality to

Table *Appearance and increasing complexity of the principal sulci noted in each plane with increasing maturity*[3 4 7]

Midsaggital	*Tangential*	*Coronal*
0 Calcarine and posterior calcarine sulci already present. Absent cingulate sulcus	0 Smooth cerebral hemispheres. Lateral sulcus wide open	0 Wide open appearance of lateral sulci
1 Calcarine and posterior calcarine sulci more apparent. First appearance of cingulate sulcus	1 Central sulci may appear. Lateral sulcus closing	1 Early closure of lateral sulci (apposition of parietal and temporal lobes)
2 Cingulate sulcus easily visible, straight and simple	2 Central and posterior central sulci visible. Lateral sulcus closed. First appearance of superior temporal sulcus	2 Further closure of lateral sulci
3 Posterior calcarine and parieto-occipital sulci more compressed. Cingulate sulcus more tortuous and now extending anteriorly	3 Lateral sulcus more tortuous with further closure. Superior temporal sulcus more apparent, inferior temporal sulcus now visible	3 Lateral sulci now fully closed
4 Cingulate sulcus more tortuous now extending posteriorly	4 Inferior temporal sulcus more apparent	4 Lateral sulci now fully closed and more tortuous with increase in size of the parietal and temporal lobes
5 Further posterior extension of cingulate sulcus. Further compression of parieto-occipital and posterior calcarine sulci	5 Superior frontal sulcus now visible	

Scoring system: 0=24–25 weeks, 5=34+ weeks.

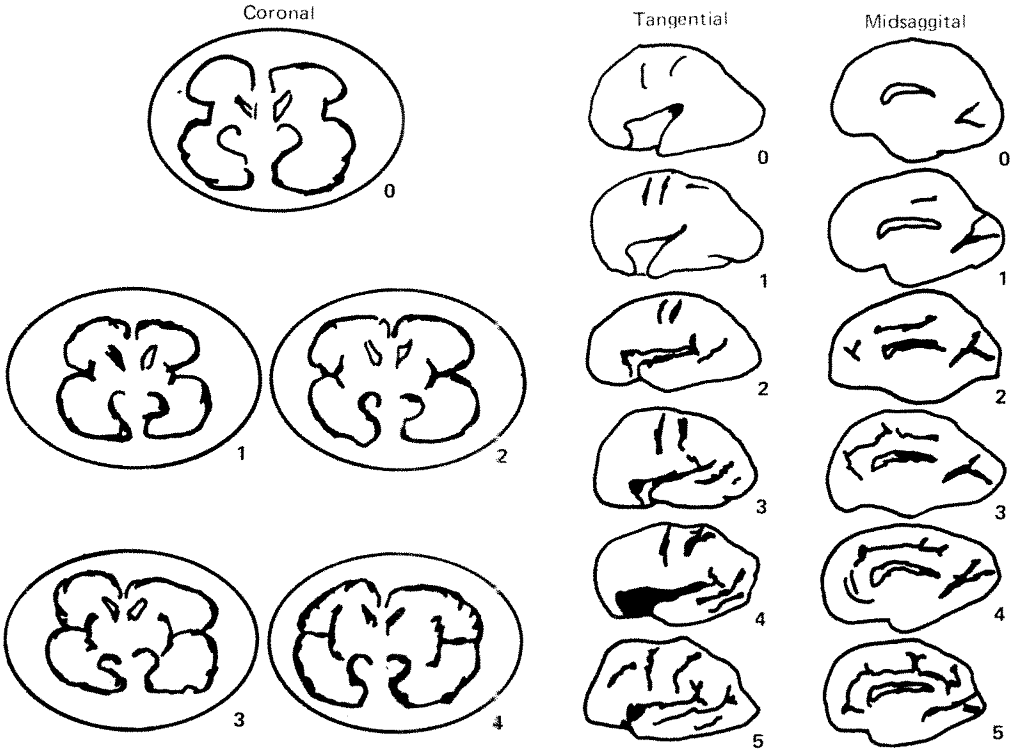


Fig 1 *Anatomical diagrams showing the increasing complexity of the principal sulci noted in each plane with increasing maturity.*[3 4 7]

permit independent assessment. The sulci that were most consistently identified with distinctive changes as maturity advanced were the precentral and postcentral and the superior and inferior temporal sulci in the tangental plane, the cingulate sulcus in the midsaggital plane, and the closure and infolding of the lateral sulcus in the coronal plane (fig 2).

The mean gestational age was 30 weeks (range 24–34). Regression lines were calculated for the scores on gestational age for each of the three observers. There was a significant positive correlation between gestational age and increasing ultrasound score for each observer ($r=0\cdot76$–$0\cdot84$, $p<0\cdot001$). One way analysis of variance (Kruskal-Wallace) among observers showed a significant association of the scores for the same subjects ($p<0\cdot01$). Fig 3 shows the same regression line for the median scores for the three observers with the 95% confidence intervals ($r=0\cdot84$). After 34 weeks' gestation weekly anatomical changes were less distinct. The study was not therefore extended beyond this point, as methods of assessing gestational age of 34 weeks or more are well established.

Discussion

Many methods have been introduced for assessment of gestational age in newborn infants.[1] All the methods have been based on studies of infants of 32 weeks' gestation or more. As standards of neonatal intensive care have advanced during the past decade, large numbers of low birthweight infants with gestational ages ranging from 24–32 weeks have survived. Because of the many clinical problems that these infants have, the application of the accepted scoring methods is difficult and often inaccurate.[2] These difficulties and inaccuracies prompted this study. Infants who require mechanical ventilation do not tolerate handling and so the use of ultrasonography, which can be carried out with minimal disturbance, is a reasonable alternative.

The principal sulci may be identified without great

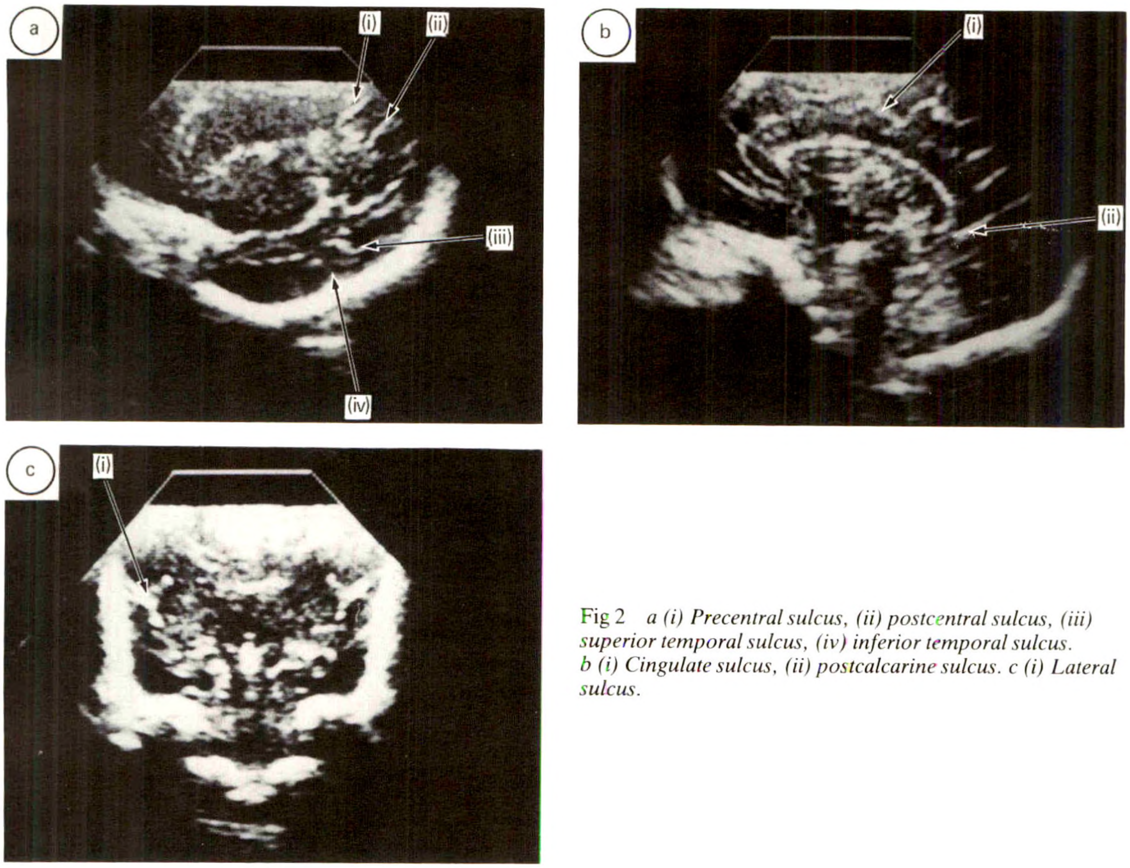


Fig 2 *a (i) Precentral sulcus, (ii) postcentral sulcus, (iii) superior temporal sulcus, (iv) inferior temporal sulcus. b (i) Cingulate sulcus, (ii) postcalcarine sulcus. c (i) Lateral sulcus.*

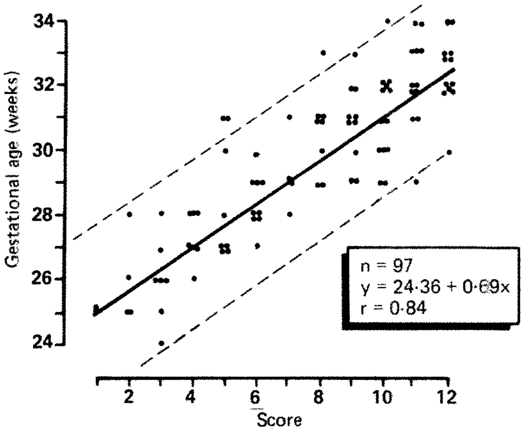


Fig 3 *Regression line of cumulative score and gestational age.*

difficulty in three planes. Some practical difficulty was encountered when the anterior fontanelle was small, but this was not common and could be overcome by repeating the scan. The use of Polaroid prints permitted independent assessment and scoring by three observers. The prints were retained as a permanent reproducible record. The scoring system showed a good correlation with the mother's menstrual history, with a linear increase in gestational age associated with increasing complexity of the brain surface marking on ultrasonography. There was, however, a wide standard deviation. The addition of more variables and perhaps the combination of ultrasonography and superficial criteria could well produce an accurate, non-invasive, and reproducible method of assessing gestational age in low birth weight infants. In addition, this technique could be used to study the effects of perinatal factors such as intrauterine growth retardation on the rate of brain maturation.

The authors wish to thank Dr MEI Morgan for her help in reading and interpreting scans. We thank Mr Ken Walters for providing the illustrations and Mrs Megan Bird for typing the manuscript.

References

[1] Dubowitz LMS, Dubowitz V. Gestational age of the newborn. Reading, Massachusetts: Addison-Wesley Publishing Company, 1977.

[2] Spinnato JA, Sibai BM, Shaver DC, Anderson GD. Inaccuracy of Dubowitz gestational age in low birth weight infants. *Obstet Gynecol* 1984;**63**:491–5.

[3] Dorovini-Zis K, Dolman CL. Gestational development of brain. *Archives of Pathological and Laboratory Medicine* 1977; **101**:192–5.

[4] Chi JG, Dooling EC, Gilles FH. Gyral development of the human brain. *Ann Neurol* 1977;**i**:86–93.

[5] Minkowski A, Larroche JC, Vigrand J, *et al.* The development of the central nervous system in early life. Philadelphia: WB Saunders, 1966:257–68.

[6] Stewart HL Jr. Duration of pregnancy and postmaturity. *JAMA* 1952;**148**:1079–83.

[7] Hamid AH. Fetal cerebral maturation in hypertensive disorders of pregnancy. *Obstet Gynecol* 1984;**63**:214–9.

[8] Campbell S. The prediction of fetal maturity by ultrasound measurement of the biparietal diameter. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1969;**76**:603–9.

Correspondence to Dr NP Murphy, Maternity Wing, Countess of Chester Hospital, Liverpool Road, Chester CH2 1BQ.

Accepted 29 July 1988

Archives of Disease in Childhood, 1989, **64,** 573–577

Chronic renal failure and growth

L REES, S P A RIGDEN, AND G M WARD

Evelina Children's Hospital, United Medical and Dental Schools, Guy's Hospital, London

SUMMARY Growth was assessed in 38 prepubertal children with chronic renal failure for a mean (range) of 2·3 (1–4) years. At first clinic visit their mean (range) glomerular filtration rate was 17 (7–35) ml/min/1·73 m^2, their mean (range) age was 3·4 (0·2–9·1) years, and 23 (61%) were greater than two standard deviations below the mean for height. After intensive medical management of their chronic renal failure, half of the children who presented before 2 years of age showed appreciable catch up growth. Only a slow improvement in growth occurred in most children presenting over 2 years of age. At final assessment, the mean (range) glomerular filtration rate was 15 (6–42) ml/min/1·73^2 and 20 (53%) were greater than two standard deviations below the mean for height. There was no correlation between glomerular filtration rate and growth. There remained a group of children who continued to grow poorly. Many of these were of low birth weight, and had dysplastic kidneys.

Growth retardation is a major problem for children with chronic renal failure.[1–4] In 1983 we set up a clinic for children with severe chronic renal failure to enable optimal management of diet, electrolyte and acid-base balance, and bone disease.[5] We have analysed the effects of intensive medical management on the growth and renal function of prepubertal children attending the clinic.

Patients and methods

All children aged less than 10 years who were prepubertal and who had attended Guy's Hospital chronic renal failure clinic for at least a year were included in the study (32 boys, six girls). The children attended the clinic at least once every three months, but most attended once every four weeks or more frequently. Most were taking energy supplements either as glucose polymers or as fat emulsions. Adequacy of diet was checked by prospective three day dietary assessments. If necessary, protein intake was adjusted so the plasma urea concentration was <20 mmol/l and serum albumin was normal. Acidosis was corrected with sodium bicarbonate. Sodium chloride supplements were gradually introduced until an improvement in growth was seen without producing oedema, hypertension, or hypernatraemia.[5] Since 1985 it has been our practice to maintain the plasma phosphate at the lower limit of the normal range for age using mild dietary phosphate restriction and calcium carbonate as a phosphate binder, and the plasma calcium at the upper limit of normal using 1,25 dihydroxycholecalciferol or 1α-hydroxycholecalciferol if necessary. We have shown this regimen to be successful in reversing and preventing secondary hyperparathyroidism.[6] Some children, however, had received aluminium hydroxide before 1985 or before attending the clinic. Infants with poor growth and energy intake were tube fed.[7] None were nephrotic or taking steroids. The children were measured using a Harpenden stadiometer by the same clinic nurse (<2 years of age, lying; >2 years, standing).

The following information was obtained from the notes:

(1) Chronological age at first clinic visit (years). The children were divided according to presentation before (group 1, n=16) or after (group 2, n=22) age 2 years. The mean (range) age of group 1 at presentation was 1·0 (0·2–1·8) and of group 2 was 5·2 (2·5–9·1) years.

(2) Height (cm) at first clinic visit and subsequently at yearly intervals. For each subject the height standard deviation score (Ht SDS) was calculated, according to the formula Ht SDS=(x–x̄)/SD, where x̄ and SD are age matched population mean height and SD respectively and x is the subject's height. Normal population data was according to Tanner *et al.*[8]

(3) Bone age at yearly intervals.[9]

(4) Calculated glomerular filtration rate (ml/min/1·73 m^2) at yearly intervals.[10]

Clinical data have been given in more detail for group 1 (table 1) because the growth changes in this group were more dramatic and variable than in group 2. There was a high incidence of low birth weight, eight being below the 10th centile. This included seven of the 10 children with renal dysplasia with or without vesicoureteric reflux. Of the other six children, all of whom had obstructed urinary tracts, only one was below the 10th centile for birth weight. Ten infants were tube fed, and nine had received aluminium hydroxide. The overall mean (SE) concentrations of plasma sodium, bicarbonate, urea, albumin, calcium and phosphate, and haemoglobin were calculated from the values at each clinic visit. We achieved our aim of maintaining plasma sodium, bicarbonate, and albumin values within normal limits, and urea under 20 mmol/l, although the haemoglobin was low in some infants. In most children the plasma calcium concentration was at the upper limit and the phosphate at the lower limit of normal, and no infants had clinical evidence of osteodystrophy.

The causes of chronic renal failure in group 2 were as follows: renal dysplasia with or without vesicoureteric reflux (n=8), obstructive uropathy (n=3), infantile polycystic kidney disease (n=3), reflux nephropathy (n=2), cystinosis (n=2), and miscellaneous (n=4).

Statistical comparisons were by the Wilcoxon rank sum test.

Results

The mean (range) Ht SDS, change from initial Ht SDS (Δ HtSDS), glomerular filtration rate, and bone age delay (bone age minus chronological age, years) at presentation and at yearly intervals are shown for groups 1 and 2 in table 2. Group 1 showed a continuing improvement in growth over the first three years despite an increasing bone age delay. Glomerular filtration rate improved continuously. In group 2, growth also improved over the first three years, again despite a progressive increase in bone age delay. Glomerular filtration rate declined slowly. There was no statistical difference in the change per year for any criteria in either group.

GROUP 1

Fig 1 shows the individual longitudinal height data for the 16 children who presented to the clinic before the age of 2 years. Twelve children were greater than 2 SD below the mean at first clinic visit, and seven of these were greater than −3 SD. Table 3 shows the results in more detail. Over the first year, eight children improved their Ht SDS (mean Δ Ht SDS 1·0, range 0·2 to 1·6), while eight grew poorly

Table 1 *Details of patients in group 1*

Patient No	*Birthweight centile*	*Diagnosis*	*Use of nasogastric tube*	*Use of aluminium hydroxide*	*Mean (SE) plasma concentration (mmol/l)*					*Mean (SE) plasma concentration (g/l)*		*No of clinic visits/year*
					Sodium	*Urea*	*Bicarbonate*	*Calcium*	*Phosphate*	*Albumin*	*Haemoglobin*	
1	50	Obstructive uropathy	−	+	140 (0·8)	16·8 (0·8)	22·0 (0·7)	2·45 (0·02)	1·51 (0·08)	43 (0·6)	118 (2)	5·0
2	75–97	Obstructive uropathy	−	−	139 (0·7)	18·9 (0·9)	22·0 (0·8)	2·42 (0·02)	1·52 (0·04)	45 (0·5)	113 (2)	6·7
3	10–25	Dysplasia (±reflux)	+	−	138 (0·5)	16·2 (0·7)	27·6 (1·4)	2·58 (0·02)	1·39 (0·06)	45 (0·7)	101 (2)	10·5
4	3–10	Dysplasia (±reflux)	−	−	138 (1·0)	10·4 (0·8)	21·1 (1·1)	2·52 (0·03)	1·58 (0·12)	43 (0·8)	124 (3)	4·0
5	3–10	Dysplasia (±reflux)	+	−	137 (0·8)	14·0 (0·7)	20·5 (0·5)	2·58 (0·03)	1·31 (0·06)	44 (0·7)	91 (3)	16·0
6	3–10	Obstructive uropathy	+	+	139 (0·8)	16·8 (1·7)	24·2 (1·5)	2·55 (0·02)	1·43 (0·09)	44 (0·6)	89 (2)	11·5
7	3	Dysplasia (±reflux)	−	−	139 (0·8)	18·2 (1·0)	21·6 (1·5)	2·56 (0·03)	1·57 (0·11)	44 (1·4)	106 (2)	4·0
8	10–25	Dysplasia (±reflux)	−	+	139 (0·4)	7·0 (0·3)	24·2 (0·5)	2·52 (0·02)	1·35 (0·03)	41 (0·4)	106 (2)	8·6
9	75–97	Obstructive uropathy	+	+	135 (0·7)	12·2 (1·0)	24·6 (0·7)	2·44 (0·03)	0·99 (0·08)	42 (0·6)	78 (1)	15·5
10	10–25	Obstructive uropathy	+	+	135 (0·6)	5·1 (0·6)	20·6 (0·9)	2·57 (0·07)	1·21 (0·06)	44 (0·7)	93 (3)	15·0
11	10–25	Dysplasia (±reflux)	+	+	137 (0·5)	17·3 (1·0)	25·3 (0·9)	2·53 (0·05)	0·88 (0·05)	45 (0·6)	69 (1)	13·0
12	3–10	Dysplasia (±reflux)	+	+	139 (0·5)	11·9 (0·7)	23·7 (0·9)	2·58 (0·03)	1·24 (0·05)	43 (0·5)	79 (1)	14·5
13	<3	Dysplasia (±reflux)	+	−	140 (0·6)	8·2 (0·4)	23·8 (0·9)	2·53 (0·08)	1·32 (0·08)	44 (0·6)	93 (4)	14·5
14	3–10	Dysplasia (±reflux)	+	−	134 (2·6)	6·1 (0·3)	22·3 (0·6)	2·62 (0·02)	1·29 (0·06)	45 (0·5)	101 (4)	17·5
15	25–50	Obstructive uropathy	+	+	142 (1·2)	11·0 (1·0)	22·0 (0·6)	2·63 (0·04)	0·91 (0·07)	43 (1·7)	93 (2)	14·0
16	3–10	Dysplasia (±reflux)	−	+	138 (0·4)	9·5 (0·6)	21·7 (0·4)	2·54 (0·02)	1·14 (0·06)	43 (0·5)	115 (1)	7·0

Table 2 *Height standard deviation score (Ht SDS), change from initial Ht SDS (△ Ht SDS), glomerular filtration rate (ml/min/1·73 m^2), and bone age delay (years) at presentation to clinic and at yearly intervals thereafter. Results are mean (range)*

	Years after presentation				
	0	*1*	*2*	*3*	*4*
			Group 1		
No of patients	16	16	14	7	5
Ht SDS	−2·9 (−4·1 to −1·5)	−2·6 (−4·3 to −0·3)	−2·4 (−4·0 to 0)	−2·0 (−3·5 to −0·1)	−2·2 (−3·3 to −0·2)
Δ Ht SDS	—	+0·3 (−1·4 to 1·6)	+0·6 (−0·8 to 2·1)	+0·9 (−0·8 to 1·8)	+0·9 (−0·6 to 1·6)
Glomerular filtration rate	17 (7–37)	18 (8–36)	18 (8–33)	21 (8–43)	22 (7–40)
Bone age delay	−0·3 (−1·2 to 0·3)	−0·6 (−1·5 to 0·5)	−0·7 (−1·5 to 0·5)	−0·8 (−1·8 to 0·1)	−1·5 (−2·1 to −0·6)
			Group 2		
No of patients	22	22	12	8	5
Ht SDS	−2·1 (−4·9 to 0·3)	−2·0 (−4·6 to 0·4)	−1·9 (−4·4 to 0·6)	−2·2 (−4·2 to 0·3)	−2·6 (−3·5 to −1·5)
Δ Ht SDS	—	+0·1 (−0·5 to 0·5)	+0·3 (−0·4 to 1·0)	+0·4 (−0·5 to 1·0)	+0·4 (−0·5 to 0·8)
Glomerular filtration rate	18 (7–35)	16 (6–29)	19 (8–26)	14 (6–21)	15 (11–25)
Bone age delay	−0·9 (−2·4 to 0·6)	−1·0 (−3·2 to 0·3)	−1·2 (−2·8 to −0·4)	−1·3 (−3·3 to −0·3)	−1·6 (−2·3 to −1·0)

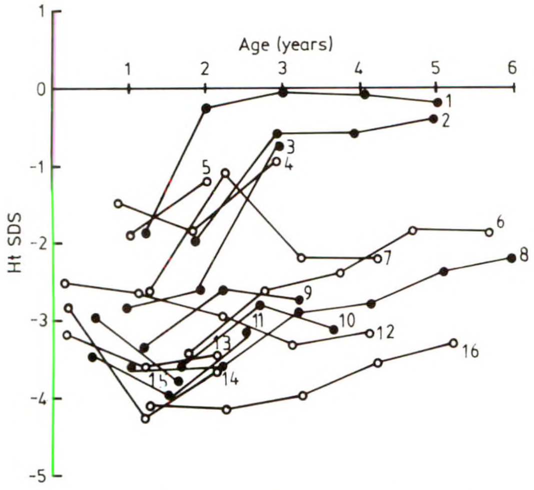


Fig 1 *Growth of 16 children (patient numbers 1–16) with chronic renal failure who presented to the clinic before 2 years of age (group 1). Birth weight <10th centile (○), birth weight >10th centile (●).*

Table 3 *Number of years studied, glomerular filtration rate (ml/min/1·73 m^2) at start and finish of the study, and change in height standard deviation score (Δ Ht SDS) over the first year, the first two years, and overall, in the 16 infants who presented to clinic before 2 years of age (group 1)*

Patient No	*No of years studied*	*Glomerular filtration rate*		*Δ Ht SDS*		
		Start	*Finish*	*Overall*	*Over one year*	*Over two years*
1	4	24	30	+1·6	+1·6	+1·8
2	3	12	13	+1·6	+1·4	+1·4
3	2	13	8	+2·1	+0·2	+2·1
4	2	37	34	+0·6	−0·4	+0·6
5	1	20	11	+0·7	+0·7	—
6	4	14	8	+1·5	+0·8	+1·1
7	3	20	20	+0·5	+1·5	+0·5
8	4	29	42	+1·2	0	+0·7
9	2	10	8	+0·6	+0·7	+0·6
10	2	24	15	+0·5	+0·8	+0·5
11	2	7	9	+0·4	−0·5	+0·4
12	4	8	7	−0·6	−0·1	−0·4
13	2	11	9	−0·3	−0·4	−0·6
14	2	13	17	−0·8	−1·4	−0·8
15	1	8	8	−1·0	−1·0	—
16	4	15	24	+0·8	−0·1	+0·1

(−0·5, −1·4 to 0). By the end of the second year, 11 children had improved their rate of growth (0·9, 0·1 to 2·1), whereas only three had failed to do so (−0·6, −0·8 to −0·4). Continuing improvement in growth occurred in five of the seven children after three years, and three of the five children after four years. Growth over the first two years was better in the children of birth weight >10th centile (1·0, 0·1 to 1·6), than in those of birth weight <10th centile (0·2, −0·8 to 1·1), but this did not reach significance. All three of the children whose growth was declining after two years were of birth weight <10th centile, and had dysplasia with or without reflux.

Six of the 10 children who were tube fed showed an improvement in their rate of growth (patients 3, 5, 6, 9, 10, 11). In two (patients 3 and 5) a dramatic effect was seen (fig 2). Previous use of aluminium hydroxide did not affect growth, nor did the number of clinic visits per year. There was no relation between the concentrations of plasma

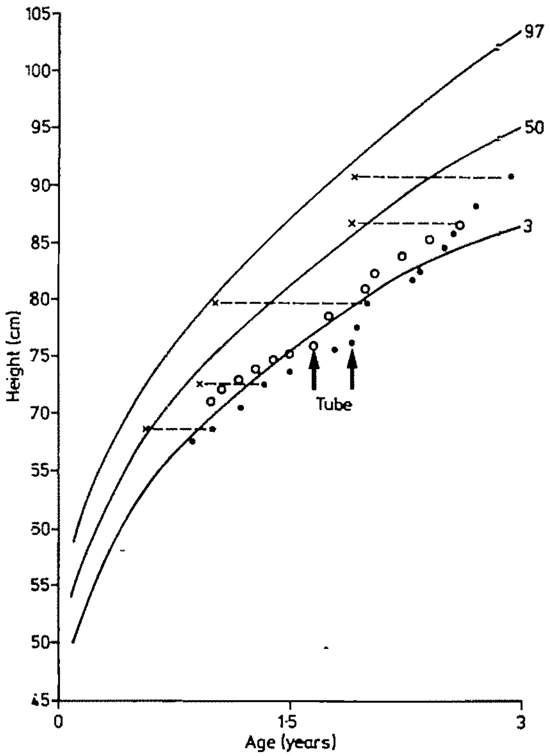


Fig 2 *Growth of two infants (patients 3 and 5, indicated by ○ and ●) with severe chronic renal failure before and after tube feeding.*

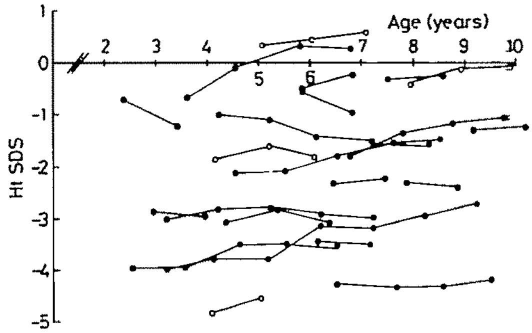


Fig 3 *Growth of 22 children with chronic renal failure who presented to the clinic after 2 years of age (group 2). Boys (●), girls (○).*

sodium, bicarbonate, urea, and albumin or the haemoglobin and growth.

GROUP 2

Fig 3 shows the individual longitudinal height data for the 22 children who presented to the clinic after the age of 2 years. Eleven were greater than 2 SD below the mean at first clinic visit, and seven of these were greater than −3 SD. Changes in rates of growth were less dramatic in this group. Thirteen children showed an improvement in Ht SDS over the first year (mean Δ Ht SDS 0·2, range, 0·1 to 1·0); in two Ht SDS remained unchanged; in seven it deteriorated (−0·2, −0·1 to −0·5). By the end of the second year, eight of the 12 children had improved their Ht SDS (0·4, 0·2 to 1·0), one remained unchanged, and two had shown a deterioration (−0·3, −0·1 to −0·4). Continuing slow improvement in growth occurred in five of the eight children after three years. Over the fourth year, Ht SDS of the five patients remained unchanged.

Four of the eight children with dysplasia with or without reflux were among the seven children greater than −3 SD below the mean for height at presentation.

There was no correlation between glomerular filtration rate and rate of growth in either group.

Discussion

The beneficial effects of early transplantation on growth,[11 12] and the recent availability of growth hormone as a therapeutic possibility, make it particularly important that the growth patterns of children with chronic renal failure should be studied. Sixty percent of our children were already below the third centile for height when they were first seen in our clinic. Other centres have reported similar findings.[2 3] The rapid growth and high energy requirements during the first two years of life make this the time when most of the adverse effect on height occurs, and fall in Ht SDS has been reported to be as high as 0·6 SD per month.[2 3 13 14] Results of treatment to induce catch up growth in children with chronic renal failure who have suffered growth delay during this critical period have been disappointing.[2–4 14] In our experience, intervention during the first two years of life can result in dramatic catch up growth. There remains a group of infants, however, who do not respond to identical medical care. Many of these are of low birth weight and have dysplasia with or without reflux. It is recognised that some infants who are light for dates at birth because of an in utero environmental insult continue to grow poorly postnatally. This is thought to be a result of impaired growth potential at the cellular level.[15] It is interesting to speculate that the environmental insult that causes dysplasia with or without reflux may also affect growth potential.

After infancy less dramatic changes in rate of growth were seen, with most children showing a slow improvement in Ht SDS. These findings are consistent with those reported from other centres.[2–4 14] The bone age delay indicates that there remains a potential for catch up growth, but it is still unknown why children with chronic renal failure do not catch up to their genetic potential. We were unable to find any correlation between the glomerular filtration rate and the rate of growth, in agreement with other reports.[2–4]

In conclusion, many children with chronic renal failure are short by the time they are seen by a paediatric nephrologist. Strict attention to diet, electrolyte and acid-base balance, and the prevention of osteodystrophy may result in dramatic catch up growth in some infants who are treated during the first two years of life. If treatment is delayed until after two years of age, a slow improvement in growth occurs in most children. There remains a group of children, however, whose growth is resistant to theoretically optimal management. Many of these are of low birth weight and have dysplasia with or without reflux. These children may benefit from an alternative approach such as transplantation before end stage renal failure is reached, or growth hormone treatment in supraphysiological doses.

References

[1] West C, Smith W. An attempt to elucidate the cause of growth retardation in renal disease. *Am J Dis Child* 1956;**91**:460–76.

[2] Kleinknecht C, Broyer M, Huot D, *et al.* Growth and development of nondialysed children with chronic renal failure. *Kidney Int* 1983;**24**:S40–7.

[3] Rizzoni G, Basso T, Setari M. Growth in children with chronic renal failure on conservative treatment. *Kidney Int* 1984;**26**: 52–8.

[4] Polito C, Greco L, Totino SF, *et al.* Statural growth of children with chronic renal failure on conservative treatment. *Acta Paediatr Scand* 1987;**76**:97–102.

[5] Rees L, Rigden SPA, Chantler C, Haycock GB. Growth and methods of improving growth in chronic renal failure managed conservatively. *Paediatric and Adolescent Endocrinology* (in press).

[6] Tamanaha K, Mak RHK, Rigden SPA, *et al.* Long-term suppression of hyperparathyroidism by phosphate binders in uremic children. *Pediatric Nephrology* 1987;**1**:145–9.

[7] Rigden SPA, Start KM, Rees L. Nutritional management of infants and toddlers with chronic renal failure. *Nutr Health* 1987;**5**:163–74.

[8] Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity: British children, 1966. Part II. *Arch Dis Child* 1966;**41**:613–35.

[9] Tanner JM, Whitehouse RH, Marshall WA, *et al. Assessment of skeletal maturity and prediction of adult height (TW2 method).* London: Academic Press, 1975.

[10] Morris MC, Allanby CW, Toseland P, *et al.* Evaluation of a height/plasma creatinine formula in the measurement of glomerular filtration rate. *Arch Dis Child* 1982;**57**:611–4.

[11] Bosque M, Munian A, Bewick M, *et al.* Growth after renal transplants. *Arch Dis Child* 1983;**58**:110–4.

[12] Rees L, Greene SA, Adlard P, *et al.* Growth and endocrine function after renal transplantation. *Arch Dis Child* 1988;**63**: 1326–32.

[13] Betts PR, Magrath G. Growth pattern and dietary intake of children with chronic renal insufficiency. *Br Med J* 1974;**ii**: 189–93.

[14] Rizzoni G, Broyer M, Guest G, *et al.* Growth retardation in children with chronic renal disease: scope of the problem. *Am J Kidney Dis* 1986;**4**:256–61.

[15] Parkin JM. The short child. In: Brook CGD, ed. *Clinical paediatric endocrinology.* Oxford: Blackwell Scientific, 1981: 113–33.

Correspondence to Dr L Rees, University Department of Paediatrics, Guy's Tower (Floor 12), Guy's Hospital, London SE1 9RT.

Accepted 6 October 1988

Archives of Disease in Childhood, 1989, **64**, 578–580

Neonatal urological ultrasound: diagnostic inaccuracies and pitfalls

N W CLARKE, D C S GOUGH, AND S J COHEN

Department of Paediatric Surgery, Booth Hall and Royal Manchester Children's Hospitals, Manchester

SUMMARY Ninety one patients with urinary tract abnormalities diagnosed before birth were reviewed. Diagnoses based on prenatal and postnatal ultrasound scans alone were compared with the final diagnoses after full urological investigations, with operative or necropsy confirmation in 79 cases. The results confirmed that ultrasound examination before birth usually detects non-specific abnormalities and although scanning after birth is more accurate it is not absolutely reliable. A diagnosis of 'multicystic kidney' made on ultrasound scan alone is especially prone to error. Such mistakes can be avoided if full urological investigation is undertaken in every case.

Patients and methods

Ninety one patients were reviewed, all of whom had antenatally diagnosed urinary tract abnormalities for which they had been referred for treatment. In order to assess the accuracy of ultrasonography both antenatal and postnatal ultrasonographic diagnoses were compared with the diagnoses made after full urological investigations had been carried out. Confirmation of the diagnoses was made at operation in 73 cases and at necropsy in six.

Antenatal ultrasound investigations undertaken at the referring hospital were carried out by experienced medical staff using different types of ultrasound scanners at various times during the pregnancy. Most of the abnormalities were detected in the late second or third trimesters of pregnancy. Referral to a paediatric urologist for treatment usually took place immediately after birth. Further scanning was undertaken after referral by experienced consultant radiologists.

All patients underwent renography and cystography, with anatomical localisation by intravenous urography and sometimes antegrade pyelography. Dimercaptosuccinic acid (DMSA) scanning was used when non-functioning systems were encountered or when localisation of functioning renal tissue was difficult. Babies with suspected lower tract problems were cystoscoped.

On full scanning the criteria for diagnosis were strictly followed. Patients with renal pelvic dilatation, functioning parenchymal tissue, and an obstructive curve on diuresis renography,[1] were diagnosed as having obstruction of the pelviureteric junction. Those with hydronephrosis, hydroureter, and an obstructed renographic appearance, were diagnosed as having obstruction of the vesicoureteric junction. Multicystic dysplasia was diagnosed if there was cystic renal dilatation in the absence of functioning parenchymal tissue on intravenous pyelography or DMSA scan, or both. Vesicoureteric reflux was diagnosed when reflux in to a dilated ureter was seen on the cystogram. Patients with urinary tract changes consistent with bladder outflow obstruction in the presence of a posterior urethral valve were diagnosed as having a posterior urethral valve, and patients were diagnosed as having a ureterocoele when one was seen on intravenous pyelography or at cystoscopy. All other cases were deemed to have non-specific upper tract dilatation with the exception of those grouped under the heading miscellaneous in table 1.

Results

Ninety one patients were studied, all of whom had abnormalities of their urinary tracts. The results are shown in table 1.

The commonest abnormality was obstruction of the pelviureteric junction (n=35, 38%). Of these four were bilateral, two had associated vesicoureteric reflux, two had contralateral multicystic kidneys and one had contralateral renal agenesis.

There were also 17 patients with unilateral multicystic kidneys, nine with posterior urethral valves, eight with obstruction of the vesicoureteric junction,

Table 1 *Final diagnosis, and number correctly diagnosed by ultrasound scanning and full radiological screening*

Diagnosis	*Total No of patients*	*No correctly diagnosed by ultrasound scanning*		*No correctly diagnosed by full radiological screening*
		Before birth	*After birth*	
Obstruction of the pelviureteric junction	35	5	14	35
Multicystic kidney	17	9	14	17
Posterior urethral valves	9	6	7	9
Obstruction of the vesicoureteric junction	8	0	0	8
Ureterocoeles	7	0	3	7
Vesicoureteric reflux	5	0	0	5
Non-specific dilatation	4	4	4	4
Miscellaneous	6	4	4	6

seven with ureterocoeles, five with vesicoureteric reflux, and four with non-specific ureteric dilatation. There were six patients in the group labelled miscellaneous; these comprised two patients with unilateral renal agenesis, one with infantile polycystic disease, one with a persistent cloaca, one with an abdominal neuroblastoma, and one with bilateral ureteric stenosis.

Table 1 shows the number of correct diagnoses made within each subgroup when each of the three different investigations was used. The antenatal ultrasound scan was insufficiently specific or accurate to make a firm diagnosis in any of the babies with vesicoureteric reflux, vesicoureteric obstruction, or ureterocoele. Accuracy improved for multicystic kidneys and posterior urethral valves (nine of 17 and six of nine babies, respectively, being correctly diagnosed), but was still poor in obstruction of the pelviureteric junction (five in 35 cases). In the miscellaneous group the patients with abdominal neuroblastoma, infantile polycystic kidney, and unilateral renal agenesis had definitive diagnoses made on the antenatal scan.

When patients were investigated by postnatal ultrasound scanning there was a considerable increase in diagnostic accuracy in multicystic kidney (14 of 17) and a moderate improvement in posterior urethral valves, obstruction of the pelviureteric junction and ureterocoeles (seven of nine, 14 of 35, and three of seven, respectively). Obstruction of the vesicoureteric junction and vesicoureteric reflux were not diagnosed in any case, confirming that ultrasound scanning was as imprecise postnatally as it was antenatally for these conditions. In the miscellaneous group the diagnostic accuracy was the same for both prenatal and postnatal ultrasonography.

The diagnosis was completely accurate in all the subgroups after full screening. Further confirmation of the diagnosis was made in 73 patients who underwent surgical correction, and in a further six who came to necropsy. These patients died either from irreversible renal failure secondary to urinary tract obstruction, or from associated cardiopulmonary abnormalities. In all patients the diagnosis made after full screening corresponded with that made at operation or necropsy.

Table 2 *Number of patients misdiagnosed as having multicystic kidney by ultrasound scanning*

Correct diagnosis	*No misdiagnosed before birth*	*No misdiagnosed after birth*
Obstruction of the pelviureteric junction	8	6
Ureterocoele	3	2
Obstruction of the vesicoureteric junction	2	1

Among the patients a number of anomalies were misdiagnosed on ultrasonography as multicystic kidney. There were 13 antenatally and nine postnatally. The actual diagnosis was only determined after full urological screening. The results are shown in table 2. The differentiation between obstruction at the pelviureteric junction and multicystic kidney presented the greatest difficulty, but there was also difficulty in diagnosing ureterocoeles and obstruction at the vesicoureteric junction.

Discussion

The accuracy of antenatal ultrasound scanning in diagnosing abnormalities of the urinary tract has been discussed by several authors. Avni *et al* claimed to have correctly diagnosed 43 out of 63 fetal uropathies.[2] Grignon *et al*[3] found an 'accuracy' of 77% when considering obstruction at the pelviureteric junction and Turnock and Shawis[4] made accurate diagnoses in 19 out of 32 children with various urological abnormalities. The definition of the word accurate, however, must be carefully considered as the ultrasound findings (particularly in the latter two groups) were mainly non-specific and in Turnock and Shawis' series 12 of 24 diagnoses of pelviureteric obstruction were incorrect. Two further series confirm these findings: Hutson *et al* claimed an accuracy of 89%.[5] When their results are analysed, however, only three of the cases had been given a specific diagnosis; the actual abnormality was defined in only 17% of their total cases. Pocock *et al* claim 26 out of 30 patients had correctly diagnosed abnormalities, but their results show that over half their cases had the non-specific finding of 'hydronephrosis'.[6] Among these cases there was a broad range of disease including obstruction of the pelviureteric and vesicoureteric junctions, multicystic dysplasia, and ureterocoeles, all abnormalities with different treatments and varying prognoses. Their all encompassing statement that antenatal ultrasound 'accurately diagnoses fetal abnormalities' is not strictly true; although a finding of hydronephrosis or cystic enlargement may be a sign of underlying obstruction, dysplasia, or reflux it is not sufficiently accurate a diagnosis for initiating treatment or commenting on prognosis.

Once an abnormality is detected the first priority is to confirm the diagnosis.[7] Postnatal ultrasound scanning has an important part to play, but as our results show it must not be used alone. Although the detection of intrarenal dilatation using ultrasound has a high degree of accuracy,[8] dilatation does not equal diagnosis, merely being an indication for further investigation. We feel that full investigation should be mandatory, but we have found series in which ultrasound scanning has been the only imaging technique used. Although we accept that accuracy will vary according to the operator and the type of machine, we believe that to make a diagnosis from the ultrasound scan alone will necessarily mean that there is an unacceptable degree of speculation in many cases.

The difficulty in differentiating multicystic dysplasia from obstruction of the pelviureteric junction has been emphasised before.[9 10] Avni failed to distinguish between these two diagnoses in four of nine cases in his series (45%).[2] We found this a problem in 15% of our cases with obstruction at the pelviureteric junction, but we also encountered difficulty with other abnormalities such as ureterocoeles. Errors of this type were present in 9% of our series. As the current vogue in some hospitals is to establish the diagnosis by ultrasound alone there is a serious danger that a number of cases will be misdiagnosed with the attendant possibilities of increased kidney damage and morbidity.

We have recently had a patient who was diagnosed as having multicystic dysplasia, and who was managed conservatively on the basis of the ultrasonographic diagnosis alone. He subsequently presented to us with posterior urethral valves at the age of 6 months. Examples such as this, though they are the exception rather than the rule, are bound to occur with greater frequency if too much reliance is placed on postnatal ultrasound scanning without full investigation. In the words of one investigator[11]: 'The inability of ultrasound to delineate the exact anatomy of all lesions is to be anticipated but is often not considered'. We feel that full investigation should take place, not only in patients with multicystic dysplasia on ultrasound scan, but in patients in whom an anatomical abnormality of the urinary tract has been detected antenatally.

References

[1] O'Reilly PH, Testa HJ, Lawson RS, *et al.* Diuresis renography in equivocal urinary tract obstruction. *Br J Urol* 1978;**50**:76–80.

[2] Avni EF, Rodesch F, Schulman CC. Fetal uropathies: diagnostic pitfalls and management. *J Urol* 1985;**134**:921–5.

[3] Grignon A, Filiatrault D, Homsy Y, *et al.* Ureteropelvic junction stenosis: antenatal ultrasonographic diagnosis, postnatal investigation and follow-up. *Radiology* 1986;**160**:649–51.

[4] Turnock RR, Shawis R. Management of fetal urinary tract abnormalities detected by prenatal ultrasonography. *Arch Dis Child* 1984;**59**:962–5.

[5] Hutson JM, McKenzie JR, Young DG, *et al.* Antenatal diagnosis of surgical disorders by ultrasonography. *Lancet* 1985;**i**:621–3.

[6] Pocock RD, Whitcombe JB, Andrews S, *et al.* Outcome of antenatally diagnosed urological abnormalities. *Br J Urol* 1985;**57**:788–92.

[7] Thomas DFM. Urological diagnosis in utero. *Arch Dis Child* 1984;**59**:913–5.

[8] Hederstrom E, Forsberg L. Accuracy of ultrasound compared with urography in detection of intrarenal dilatation in children. *Acta Radiol Diagn* 1985;**26**:201–7.

[9] Diament MJ, Fine RN, Ehrlich R, Kangarloo H. Fetal hydronephrosis: problems in diagnosis and management. *J Pediatr* 1983;**103**:435.

[10] Felson B, Cussen LJ. The hydronephrotic type of unilateral congenital multicystic disease of the kidney. *Semin Roentgenol* 1975;**10**:113–23.

[11] Rutledge JC, Weinberg AG, Friedmann JH, *et al.* Anatomic correlates of ultrasonographic prenatal diagnosis. *Prenat Diagn* 1986;**6**:51–61.

Correspondence to Mr N W Clarke, Department of Urology, Withington Hospital, West Didsbury, Manchester M20 8LR.

Accepted 9 August 1988

Archives of Disease in Childhood, 1989, **64,** 581–586

Single dose trimethoprim for urinary tract infection

T NOLAN,* L LUBITZ,† AND F OBERKLAID‡

**Melbourne University Department of Paediatrics, and †Departments of General Paediatrics and ‡Ambulatory Paediatrics, Royal Children's Hospital, Parkville, Victoria, Australia*

SUMMARY A randomised clinical trial of single dose trimethoprim against a seven day course of co-trimoxazole (trimethoprim/sulphamethoxazole) for the treatment of uncomplicated urinary tract infection was carried out in 106 children aged between 2 and 16 years. Of the 50 children with confirmed urinary tract infections who were followed up 48 hours after treatment with a single dose of trimethoprim all were free of infection, whereas two of the 56 who received the course of co-trimoxazole (4%) had persisting infections. At follow up after 10 days, however, significantly more of the group treated with trimethoprim had evidence of recurrent urinary tract infection compared with those who had received co-trimoxazole (10 of 44, 23%, compared with one of 46, 2%). Of the recurrences in the trimethoprim group, six were asymptomatic.

We conclude that single dose trimethoprim is effective in clearing the urine of bacteria, but the risk of asymptomatic bacteriuria soon after treatment is high.

The use of a single dose or a single day of treatment for uncomplicated urinary tract infections in children has obvious attractions.[1] These include improved compliance, more rapid resolution of symptoms, less risk of side effects, and reduced cost.[2–4]

Previous reports have suggested that a single dose is equally as effective as a longer course, but recent reappraisal has raised the question of inadequate sample size and the committing of the Type II error—the false assumption that the two treatments were equally effective when too few patients had been studied to be sure that even quite large differences had not been missed by chance.[4 5] Moffat *et al* concluded after reviewing published clinical trials in children that there was insufficient evidence to advocate the use of short courses of treatment for urinary tract infections (Moffat M. Short course antibiotic therapy of urinary tract infections in children. Presented at the Annual Scientific Meeting of the Ambulatory Pediatric Association, Washington DC, May 1986).[5] An additional problem is that early recurrence of infection may be more likely to occur after single dose treatment.[6]

Many antibiotics have been used in single dose treatment. Several trials have evaluated trimethoprim alone in the treatment of adult urinary tract infections, and concluded that it was as effective as co-trimoxazole (trimethoprim/sulphamethoxazole) when used in conventional courses.[7–9] The rationale for the use of trimethoprim without sulphamethoxazole is the decreased risk of side effects,[9] the reduced risk of the development of resistance,[10] the reduced cost, and the elimination of an unnecessary drug from the regimen.[11] No comparison that we know of has been made of trimethoprim and co-trimoxazole, nor has trimethoprim been used as a single dose in the treatment of uncomplicated urinary tract infections.

Our hypothesis was that in children and adolescents a single dose of trimethoprim was no less effective than a seven day course of co-trimoxazole in the early eradication of urinary tract infection, reducing the risk of early recurrence, and achieving early resolution of symptoms.

Patients and methods

Patients studied were outpatients presenting to the primary care or emergency departments of the Royal Children's Hospital. They were entered into the trial if they had a urinary tract infection on clinical assessment or microscopic examination of the urine, or both. Informed consent was obtained from the parents, and the following were excluded: those known or thought to be sensitive to sulphonamides, those with persistent vomiting or any other reason for not being able to tolerate oral treatment, those with ileostomies or ureterostomies, those already on antimicrobial treatment, and those aged less than 6 months.

A total of 254 patients were eligible, and were randomised in blocks within strata related to age (6–47 months, 48 months or older) and whether or not they had had previous urinary tract infections. Of these, 138 (54%) were subsequently excluded because urinary tract infection was not confirmed by culture (n=112), they failed to attend for follow up (n=9), the organism cultured was resistant to trimethoprim or sulphamethoxazole (n=8), they were entered into the study more than once (n=7), or they were unable to take the drugs (n=2). The characteristics of the remaining 116 patients are shown in table 1. All but one patient in each group had symptoms including nausea, vomiting, urgency, frequency, dysuria, haematuria, or abdominal, back, or loin pain. Almost half the children had at least one of the following symptoms or signs: fever greater than 38°C, loin pain, back pain, or vomiting. More children receiving co-trimoxazole (35, 57%) had at least one of these signs than in the single dose group (22, 41%).

Table 1 *Characteristics of patients*

	Single dose trimethoprim (n=54)	*Co-trimoxazole twice daily for seven days (n=62)*
Mean (SD) age (months)	81 (33·2)	83 (38·1)
Range	24–180	28–188
No of girls (%)	48 (89)	52 (84)
No of boys (%)	6 (11)	10 (16)
No (%) who had had a previous urinary tract infection	18 (33)	24 (39)
No (%) with abnormal intravenous pyelogram	6/52 (12)	13/60 (22)
No (%) with abnormal micturating cysto-urethrogram	16/40 (40)	15/43 (35)

Confirmation of the diagnosis required a growth of more than 10^8 colonies/l in a midstream specimen of urine, or any growth from a suprapubic aspirate. Absence of infection was confirmed by a growth of less than 10^7 colonies/l from a midstream or bag specimen, or a sterile suprapubic aspirate. A mixed growth of organisms of 10^7 colonies/l or more was considered to be indeterminate, as was a pure growth of 10^7 colonies/l or more from a bag specimen. Those with uncertain diagnoses were withdrawn from further analysis, and when these occurred at follow up they were recorded as missing values (fig 1). There were no significant differences between the groups in the type of organisms isolated at the time of entry into the study, the most common organisms being *Escherichia coli* (75%), *Klebsiella* spp (5%), and *Proteus* spp (3%).

Trimethoprim was prepared as a powder from 300 mg tablets supplied by the manufacturer and given at the time of randomisation according to the regimen given in table 2 as a single dose in aqueous suspension under the supervision of nursing or pharmacy staff. A seven day course of co-trimoxazole was dispensed either as elixir or tablets

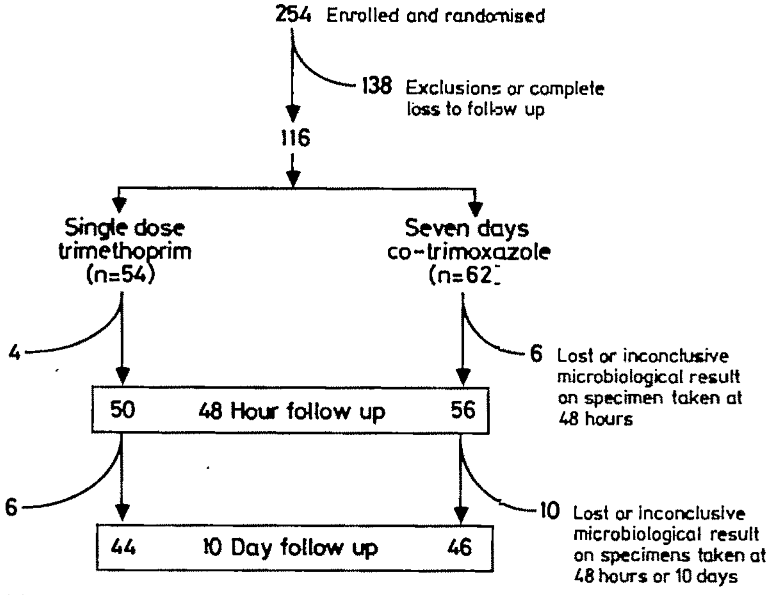

254 Enrolled and randomised
138 Exclusions or complete loss to follow up
116
Single dose trimethoprim (n=54)
Seven days co-trimoxazole (n=62)
4
6 Lost or inconclusive microbiological result on specimen taken at 48 hours
50
48 Hour follow up
56
6
10 Lost or inconclusive microbiological result on specimens taken at 48 hours or 10 days
44
10 Day follow up
46

Fig 1 *Study protocol.*

to be taken at home, and the parents were instructed to start the treatment immediately.

Patients were seen 48 hours and 10 days after randomisation and had further specimens of urine taken. All those who had not previously had a radiograph of the urinary tract had an intravenous pyelogram. In addition, those aged 7 years or younger had a micturating cystourethrogram one to three weeks after diagnosis. The study was carried out before renal ultrasonography had become a routine investigation.

Statistical analysis was by the Mantel-Haenszel test, and estimates of the risk ratio and its 95% confidence interval were calculated for infection rates in the single dose group compared with the seven day treatment.[12 13] Assignment strata (age and past history or urinary tract infection) were used. The 95% confidence intervals were calculated for the difference in risk of recurrence.

Results

The results of treatment are shown in table 3. Of the 50 patients with confirmed urinary tract infections who received a single dose of trimethoprim all were free of infection after 48 hours, whereas two of 56 (4%) of those who were receiving a seven day course of co-trimoxazole still had evidence of infection ($p=0{\cdot}26$, 95% confidence interval on the difference −9% to 1%). One of the two children with persistent infection had unilateral hydronephrosis. At the 10 day follow up of the patients in whom the presence or absence of urinary tract infection had been confirmed at 48 hours, however, 10 in the trimethoprim group (23%) compared with only one in the co-trimoxazole group (2%) had microbiological evidence of urinary tract infection ($p=0{\cdot}004$). Patients treated with a single dose of trimethoprim were 11·5 times more likely to have an early recurrence than those given a seven day course of co-trimoxazole (risk ratio 95% confidence interval 2·2 to 60·3). Neither age nor history of urinary tract infection had any effect on recurrence rates ($p=0{\cdot}31$, Breslow-Day test[14]).

Only four of the 10 patients in the trimethoprim group who had a recurrence of infection had any symptoms (table 4). Because it was not possible to type organisms it was not possible to differentiate relapse from reinfection. In only two patients, however (one from each group), was a different organism responsible for the recurrence. The only organism that was resistant to trimethoprim and sulphamethoxazole was the *Streptococcus faecalis* that was responsible for the recurrence in one patient who had received the seven day course. None of the patients who had recurrences had had loin tenderness or fever at the initial presentation.

Two thirds of the children who entered the study with confirmed urinary tract infections had not previously had infections, and eight of the 10 recurrences in the single dose group were in patients who had not previously had urinary tract infections. The child who had a recurrence in the co-trimoxazole group had had previous urinary tract infections.

More patients in the single dose group were symptom free or improved by the 48 hour follow up (47/50, 94%, compared with 46/56, 82%; $p=0{\cdot}05$). There was, however, no difference between the groups in those who were totally symptom free (61% and 62%, respectively, $p=0{\cdot}92$). Of the 10 children who had recurrences in the trimethoprim

Table 2 *Treatment regimens*

Age (years)	*Single dose trimethoprim (mg)*	*Co-trimoxazole twice daily for seven days (mg)*
<2	75	20/100
2–5	150	40/200
6–11	300	80/400
>12	450	160/800

Table 3 *Results at follow up after 48 hours and 10 days. Results at 10 days refer only to subjects in whom the presence or absence of infection was confirmed at 48 hours*

Results	*Single dose trimethoprim No (%)*	*Co-trimoxazole twice daily for seven days No (%)*	*p Value*
48 hours:			
Urinary tract infection	0	2 (4)	
No urinary tract infection	50 (100)	54 (96)	0·26
10 Days:			
Urinary tract infection	10 (23)	1 (2)	
No urinary tract infection	34 (77)	45 (98)	0·004*

*Risk ratio 11·5, 95% confidence interval 2·2 to 60·3.

Table 4 *Details of patients with recurrent infections*

Case No	*Sex*	*Treatment group*	*Age (years)*	*Symptoms*	*Initial organism isolated*	*Subsequent organism isolated*	*Micturating cystourethrogram*
1	Female	Trimethoprim	7	Symptom free	*E coli*	*E coli*	Not done
2	Female	Trimethoprim	5	Nausea, vomiting, urgency, dysuria, frequency	*E coli*	*E coli*	Mild reflex
3	Female	Trimethoprim	8	Symptom free	*E coli*	*E coli*	Normal
4	Female	Trimethorpim	3	Symptom free	*E coli*	*E coli*	Intrarenal reflux without dilatation
5	Female	Trimethoprim	8	Symptom free	*Citrobacter* spp	*Citrobacter* spp	Normal
6	Female	Trimethoprim	4	Nausea, vomiting	*E coli*	*E coli*	Normal
7	Female	Trimethoprim	8	Urgency, dysuria, frequency	*Staphylococcus saprophyticus*	*Staphylococcus saprophyticus*	Not done
8	Male	Trimethoprim	11	Symptom free	*Proteus* spp	*Proteus* spp	Normal
9	Female	Trimethoprim	6	Symptom free	*E coli*	*E coli*	Moderate reflux
10	Female	Trimethoprim	6	Urgency, dysuria, frequency	*E coli*	*Proteus*	Normal
11	Female	Co-trimoxazole	8	Symptom free	*E coli*	*S faecalis*	Normal

group four still had symptoms at 48 hours, though in three these had improved. The one patient who had a recurrence in the co-trimoxazole group had no symptoms at 48 hours. The only adverse effect that was seen was at the 10 day follow up was in one child who had received co-trimoxazole who developed ulcers in the mouth.

Discussion

These results suggest that treatment of uncomplicated, symptomatic urinary tract infections in children by a single dose of trimethoprim effects a cure rate at 48 hours similar to that achieved with a conventional seven day course of co-trimoxazole, but that this is accompanied by an unacceptably high risk of local recurrence (often without symptoms). There is a higher rate of symptomatic improvement after 48 hours, but there is little overall difference in the rate of resolution of symptoms compared with the results after a conventional seven day course.

We do not know whether the higher risk of recurrence is caused by inadequately treated (perhaps parenchymal) infection, or reinfection with the same or a different organism.[15] If the risk of recurrence is associated with a more established infection, a rapid diagnostic test to determine whether the patient has infection of the upper or lower renal tract could permit selective treatment with a single dose. Such a test, however, is not available. As none of the patients who had recurrences had both fever and loin tenderness at presentation one could speculate that reinfection rather than relapse was the most likely. Because of the unreliability of these clinical signs in localising the site of infection, however, firm conclusions cannot be drawn. It is noteworthy that the recurrences were mainly in children who had not previously had urinary tract infections, and who did not have structural abnormalities.

From these results it could be argued that trimethoprim without sulphamethoxazole is less effective than the combination. There were, however, no signs of urinary tract infection in patients in the trimethoprim group at 48 hours. In addition, it is doubtful whether synergy between trimethoprim and sulphamethoxazole is possible at the concentrations that can be achieved in urine.[16] Because the inhibitory action of sulphamethoxazole is dependent on the size of the inoculum it takes several cycles of cell growth to exhaust the microbial folate supplies, whereas trimethoprim causes rapid deprivation of the thymidilate supply to the organisms leading to the abrupt termination of folate synthesis. It is therefore probable that if there is any therapeutic effect from a single dose of co-trimoxazole, it will be from the trimethoprim component.[11 17]

Because of a flaw in the design of the study it is difficult to interpret the differences in recurrence rates. Because the urine was cultured 48 hours and 10 days after treatment was started rather than after it had finished, we could have underestimated the recurrence rate in the co-trimoxazole group. The recurrence rate in the single dose group of 23%, however, remains striking, and evidence from other trials suggests that an unbiased rate would still have been far below that in the single dose group.[2 6 18–21] The average recurrence rate in these six studies in patients given conventional courses was 9%.

Further data extracted from these studies provide additional evidence that single dose treatment is more likely to be associated with early recurrence. Fig 2 shows the results of these trials plotted to show the confidence intervals of the difference in risk of

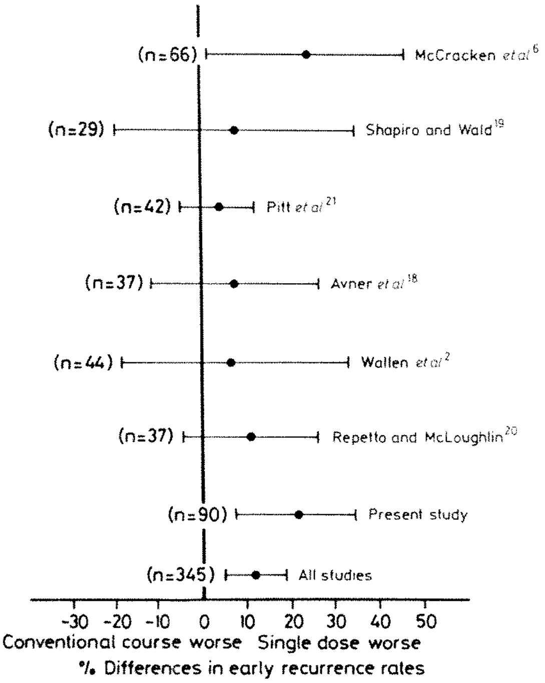


Fig 2 *Differences in risk of early recurrence and their 95% confidence intervals from published clinical trials of single dose compared with conventional treatment.*

recurrence between single dose and conventional treatment. The antibiotics used as single agents were: amoxycillin,[18 19] a cephalosporin,[6 20] amikacin,[2] and co-trimoxazole.[21] Rates of recurrence were assessed between five days and three months. Despite the diversity of antibiotics and lengths of follow up there is a striking unanimity of results in favour of the seven day course of antibiotic. Because of the small sample sizes, however, the results were significant only in the present study and in that of McCracken *et al.*[6]

The average difference in risk of recurrence between single dose and conventional treatment in these studies is 12% (95% confidence interval of the true value 5% to 19%; this is a sample size weighted calculation by the method of Gilbert *et al*[22]). This means that for every 100 children treated with a single dose of an antibiotic for an uncomplicated urinary tract infection, between five and 19 would have an early recurrence of that infection that would not have occurred if they had had seven day courses.

Single dose treatment has been advocated in the past with the caveat that close monitoring of the response to treatment is important.[23] The results of this study and others emphasise that the risk of asymptomatic recurrence should be borne in mind. We believe that there is now sufficient evidence to suggest that treatment of uncomplicated urinary tract infections with a single dose of an antibiotic should only be undertaken with caution, and with proper follow up. There is evidence in adult patients that failure of a single dose is more likely to result in failure of a subsequent course of treatment than if the initial failure had followed a course of treatment.[24] Our results are mainly from young children (only three were over the age of 12) and it may be that the use of a single dose in children who are not at risk of acquiring renal scars would be appropriate; again, close follow up would be essential.

The combination of a high initial dose and a conventional course may effect more rapid symptomatic improvement without the risk of early recurrence of infection.

We thank Drs Peter Loughnan, Harley Powell, Jill Sewell, and Jan Cullen, together with an anonymous reviewer, for assistance and helpful criticism. We also thank the nurses in the department of ambulatory paediatrics for their enthusiastic cooperation, and Wellcome Australia for supplying the trimethoprim.

References

[1] Ogra PL, Faden HS. Urinary tract infections in childhood: an update. *J Pediatr* 1985;**106:**1023–9.

[2] Wallen MD, Zeller WP, Goessler M, Connor E, Yogev R. Single-dose amikacin treatment of first childhood E coli lower urinary tract infections. *J Pediatr* 1983;**103:**316–9.

[3] Fine JS, Jacobsen MS. Single-dose versus conventional therapy of urinary tract infections in female adolescents. *Pediatrics* 1985;**75:**916–20.

[4] Shapiro ED. Short course antimicrobial treatment or urinary tract infections in children: a critical analysis. *Pediatr Infect Dis* 1982;**1:**294–7.

[5] Moffatt M, Embree J, Grimm MD and Law B. Short course antibiotic therapy for urinary tract infections in children: a methodological review of the literature. *Am J Dis Child* 1988;**142:**57–61.

[6] McCracken GH, Ginsburg CM, Namasonthi V, Petruska M. Evaluation of short-term antibiotic therapy in children with uncomplicated urinary tract infections. *Pediatrics* 1981;**67:** 796–801.

[7] Brumfitt W, Pursell R. Double-blind trial to compare ampicillin, cephalexin, cotrimoxazole and trimethoprim in the treatment of urinary infection. *Br Med J* 1972;**ii:**673–6.

[8] Koch UJ, Schumann KP, Kuchler R, Kewitz H. Efficacy of trimethoprim, sulfamethoxazole and the combination of both in acute urinary tract infections: clinical and pharmacokinetical studies. *Chemotherapy* 1973;**19:**314–21.

[9] Lacey RW, Lord VL, Gunasekera HKW, Leiberman PJ, Luxton DEA. Comparison of trimethroprim alone with trimethoprim-sulfamethoxazole in the treatment of respiratory and urinary infections with particular reference to selection of trimethoprim resistance. *Lancet* 1980;**i:**1270–3.

[10] Anonymous. Bacterial resistance to trimethoprim. [Editorial.] *Br Med J* 1980;**ii:**571–2.

[11] Anderson JD, Lacey RW, Lewis EL, Sellin MA. Failure to demonstrate an advantage in combining sulfamethoxazole with

trimethoprim in an experimental model of urinary infection. *J Clin Pathol* 1974;**27**:619–22.

[12] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *JNCI* 1959;**22**:719–8.

[13] Green SB, Byar DP. The effect of stratified randomization on size and power of statistical tests in clinical trials. *J Chronic Dis* 1978;**31**:445–54.

[14] Breslow NE, Day NE. Statistical methods in cancer research. Vol 1. *The analysis of case control studies*. Lyon: International Agency for Research on Cancer, 1980.

[15] Tolkoff-Rubin NE, Rubin RH. Single dose treatment of acute uncomplicated infections defined by the antibody-coated bacteria assay. In: Bailey RR, ed. *Single dose therapy of urinary tract infection.* Sydney: ADIS Health Science Press, 1983:42–52.

[16] Greenwood D. Relevance of in vitro synergy to therapy does synergy between diaminopyridines and sulfonamides operate at concentrations achievable in the urine? *J Antimicrob Chemother* 1979;**5**(suppl B):85–9.

[17] O'Grady F. Single dose treatment of urinary tract infection: a microbiologist's view. In: Bailey RR, ed. *Single dose therapy of urinary tract infection.* Sydney: ADIS Health Science Press, 1983:79–81.

[18] Avner Ed, Inglefinger JR, Herrin JT, *et al.* Single-dose amoxicillin therapy of uncomplicated pediatric urinary tract infections. *J Pediatr* 1983;**102**:623–7.

[19] Shapiro ED, Wald ER. Single-dose amoxicillin treatment of urinary tract infections. *J Pediatr* 1981;**99**:989–92.

[20] Repetto HA, MacLoughlin GJF. Single dose cefotaxime in the treatment of urinary tract infections in children: a randomised clinical trial. *J Antimicrob Chemother* 1984;**14**(suppl B):307–10.

[21] Pitt WR, Dyer SA, McNee JL, Burke JR. Single dose trimethoprim-sulfamethoxazole treatment of symptomatic urinary infection. *Arch Dis Child* 1982;**57**:229–31.

[22] Gilbert JP, McPeek B, Mosteller F. Progress in surgery and anesthesia: benefits and risks of innovative therapy. In Bunker J, ed. *Costs, risks and benefits of surgery*. New York: Oxford, 1977.

[23] Smith AL. Editorial. *Pediatr Alert* 1982;**7**:4.

[24] Rubin RH, Fang LST, Jones SR, *et al.* Single dose amoxycillin therapy for urinary tract infection. *JAMA* 1980;**244**:561–564.

Correspondence to Dr T Nolan, University of Melbourne Department of Paediatrics, Royal Children's Hospital, Parkville, Victoria 3052, Australia.

Accepted 26 August 1988

Archives of Disease in Childhood, 1989, **64,** 587–592

Growth hormone secretion in Turner's syndrome and influence of oxandrolone and ethinyl oestradiol

A A MASSARANO,* C G D BROOK,* P C HINDMARSH,* P J PRINGLE,* J D TEALE,† R STANHOPE,‡ AND M A PREECE‡

**Endocrine Unit, Middlesex Hospital, London, †Department of Clinical Biochemistry and Clinical Nutrition, St Luke's Hospital, Guildford, Surrey, and ‡The Department of Growth and Development, Institute of Child Health, London*

SUMMARY We investigated 24 hour growth hormone secretion by intermittent 20 minute blood sampling in 34 prepubertal patients with Turner's syndrome, aged 4·3–12·4 years. Growth hormone profiles were analysed by the PULSAR programme and results expressed as the sum of growth hormone pulse amplitudes. Six patients had abnormal growth hormone pulse frequencies. In the remaining 28, growth hormone pulse amplitudes declined significantly with increasing age, but there was no correlation between growth hormone pulse amplitudes and growth rates. Concentrations of insulin like growth factor-1 (IGF-1) rose with age but did not correlate with either growth rates or growth hormone secretion. Fifteen patients were given oxandrolone and 11 low dose ethinyl oestradiol. Both agents increased height velocity without increasing growth hormone secretion.

We conclude that the relation between growth hormone secretion and growth in Turner's syndrome is less certain than in normal children. End organ resistance is probably due to a skeletal dysplasia. Both oxandrolone and low dose ethinyl oestradiol improve the growth of girls with Turner's syndrome, but their mechanism of action remains uncertain.

Patients with Turner's syndrome are born short, grow slowly, and achieve a reduced adult stature.[1 2] Although individual cases of growth hormone deficiency have been reported in Turner's syndrome,[3] growth hormone responses to pharmacological stimuli are similar to those seen in normal short children.[4 5]

Endogenous growth hormone secretion is known to be pulsatile and may be assessed in children using intermittent blood sampling over 24 hours.[6] In some children, considerable discrepancies have been noted between the growth hormone concentrations reached on such assessments and the results of pharmacological provocation tests.[7] Tall children produce more growth hormone over 24 hours than short children,[8] and it appears to be growth hormone pulse amplitude that correlates with growth rate in otherwise normal children.[9] The periodicity of growth hormone secretion is also relevant, abnormal patterns being associated with inadequate growth.[8]

We sought to investigate the qualitative and quantitative aspects of growth hormone secretion in Turner's syndrome and to determine the effect of growth promoting agents. The anabolic steroid oxandrolone is known to increase height velocity in Turner's syndrome.[10 11] Low dose ethinyl oestradiol increases height velocity in both the short[12] and long term.[13] The effects of these treatments on growth hormone secretion in Turner's syndrome is unknown.

Patients and methods

Thirty four patients aged 4·3 to 12·4 years (median 9·1) were studied. Karyotypes, performed by culture of peripheral lymphocytes, are shown in table 1. All had phenotypic features of Turner's syndrome. None had evidence of an emotional or eating disorder. Three patients had previously received either growth hormone, oxandrolone, or ethinyl oestradiol; these drugs had been stopped at least three months previously. One was receiving thyroxine replacement treatment. All the children were prepubertal.

Subjects were admitted the evening before the commencement of sampling when a cannula was

Table 1 *Karyotypes of 34 patients with Turner's syndrome*

No of patients	*Karyotype*
22	45,X
3	46,X,Xi(Xq)
4	45,X/46,Xi(Xq)
2	45,X/46,X,r(X)
2	45,X/46,XX
1	$46,XXp^-$

inserted and kept patent with a heparin in saline solution. They were freely mobile and took meals at regular times. Blood samples (1–2 ml) were withdrawn every 20 minutes, centrifuged, separated, and the serum stored at −20°C before analysis. Specimens for assay of insulin like growth factor-1 (IGF-1) were withdrawn at 06·00.

Of the 34 patients, 26 then received growth promoting treatment. Fifteen patients, aged 4·3–12·6 years (median 10·2) received oxandrolone 1·25 mg daily, or 0·625 mg if <7 years. Eleven patients, aged 5·1–11·7 years (median 9·7) received ethinyl oestradiol 1 µg daily, or 0·5 µg if <7 years; the two eldest received 2 µg. The treatments were continued for 0·5–1·0 years. Growth hormone sampling was repeated in all patients after six to 10 weeks of treatment.

Growth hormone concentrations were measured by a solid phase immunoradiometric assay (Tandem R, Hybritech[14]), all specimens from one subject being analysed in a single batch. The lower limit of sensitivity of the assay was 0·5 mU/l. The intra-assay coefficients of variation were 10·6, 7·8, and 4·8% at 1·4, 7·1, and 26·4 mU/l respectively.

Computerised pulse analysis was performed using the PULSAR programme[15] modified for growth hormone.[9] This generates a smoothed but variable baseline and defines pulses above that baseline, by taking into account the amplitude and duration of rises and the standard deviation of the assay. We have used simple arithmetic addition of the maximum amplitude of the defined pulses to generate the statistic 'sum of peak amplitudes'.

Plasma concentrations of IGF-1 were measured by radioimmunoassay.[16] The lower limit of sensitivity of the assay was 0·03 U/ml and the coefficients of variation were 11·0, 7·2, and 7·0% at 0·15, 0·47, and 0·94 U/ml respectively.

Height was measured every three months by standard techniques using a Harpenden stadiometer. In order to account for varying height velocities at different ages, height velocity standard deviation scores (SDS) were calculated using normal data for Turner's syndrome[2] by the formula:

$$\text{SDS} = \frac{\text{x} - \text{mean}}{\text{Standard deviation}}$$

Bone ages were estimated by the TW2 method.[17]

Approval was obtained from the ethical committees of both the Middlesex Hospital and Hospital for Sick Children, Great Ormond Street, and parental consent was obtained.

Statistical analysis of trends was by Spearman's rank correlation. Effects of treatment were assessed by the Wilcoxon signed rank test. Data are expressed as mean (SD).

Results

Three sample growth hormone profiles are illustrated in fig 1. In fig 1(a) there were eight pulses in 24 hours with nocturnal accentuation of pulse amplitude. Growth hormone concentrations fell to unrecordable concentrations between pulses. Twenty eight patients had a similar pattern, which occurs in normally growing children.[8]

The profile in fig 1(b) was more disorganised, with 11 peaks, a loss of the normal dominant three hour periodicity, and an absence of a return to unrecordable concentrations. Three patients were found to have this more 'rapid' pattern.

In fig 1(c) there was a high amplitude dominant pulse and sparse growth hormone secretion for the remainder of the 24 hours. This pattern was found in three patients. With the exception of one child, pulse frequency was normal below 8·5 years of age, with five to nine identifiable peaks in 24 hours. Above this age both high and low frequencies occurred.

Age related changes in the amplitude of growth hormone secretion are illustrated in fig 2. Analysis of the sum of peak amplitudes in 28 profiles regarded as normal showed a significant decline with age (p<0·01). No decline was apparent in maximum or mean pulse amplitude.

Growth hormone secretion, as expressed by the sum of peak amplitudes, showed no significant correlation with height velocity SDS using standards for either Turner's syndrome (fig 3) or normal children. Attempts to find a correlate using growth hormone pulse frequency, amplitude of maximum growth hormone pulse, or mean growth hormone pulse amplitude were unsuccessful. The growth of those patients judged as having abnormal growth hormone profiles was variable and not obviously different from the other patients (fig 3).

Plasma IGF-1 concentrations fell at the lower end of the range for normal children (fig 4), but increased significantly with age (p<0·001). IGF-1 concentrations did not correlate with the sum of growth hormone pulse amplitudes (p>0·3) or with height velocity SDS (p>0·5). There was a strong negative correlation with height velocity (p<0·001).

EFFECTS OF TREATMENT

Despite producing a consistent and substantial improvement in height velocity (table 2(a)), oxandrolone was associated with a decrease in growth hormone pulse amplitude (fig 5) (p=0·05). Although there was no overall effect on pulse frequency, abnormal profiles seen in four patients became normal on treatment in three. Plasma IGF-1 concentrations rose significantly.

Ethinyl oestradiol also increased height velocity (table 2(b)). There was a more variable effect on growth hormone secretion and there was no overall significant change in pulse amplitude or frequency (fig 5). There was the suggestion of an association between the change in growth hormone amplitude and the change in height velocity SDS, but this

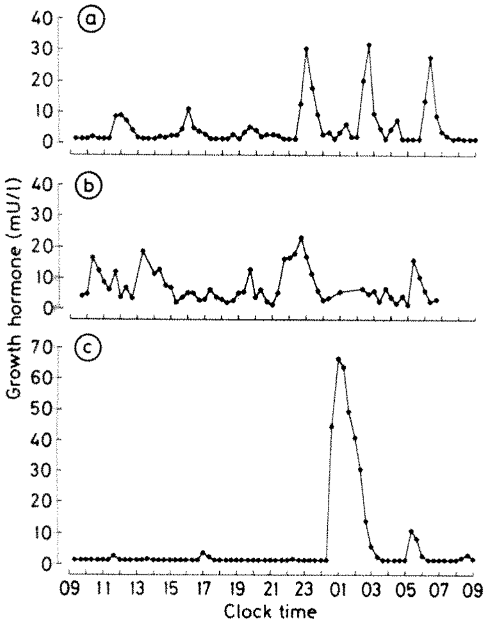


Fig 1 *Specimen 24 hour growth hormone profiles from three untreated patients with Turner's syndrome: (a) age 7·4 years; 45,X; (b) age 11·2 years; 45,X/46,X,Xi(Xq); and (c) age 8·6 years; 45,X.*

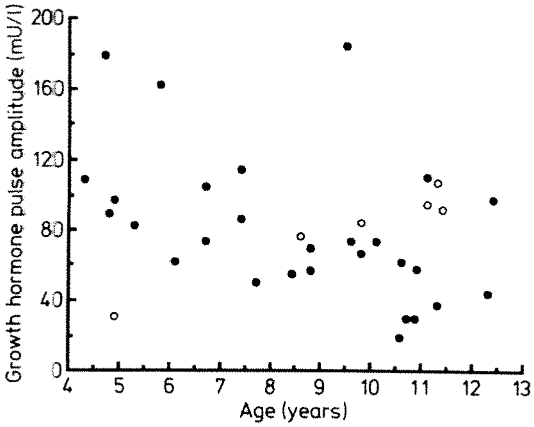


Fig 2 *Changes in sum of growth hormone pulse amplitudes with age in 34 patients with Turner's syndrome. Open symbols indicate those patients with growth hormone profiles of abnormal pattern.*

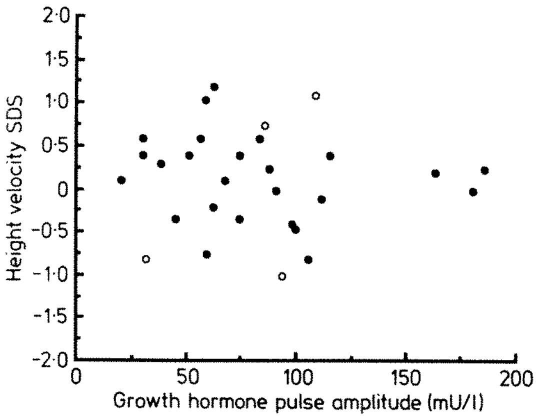


Fig 3 *Comparison of height velocity SDS (for Turner's syndrome) with sum of growth hormone pulse amplitudes in 29 patients. Open symbols indicate those patients with abnormal profiles.*

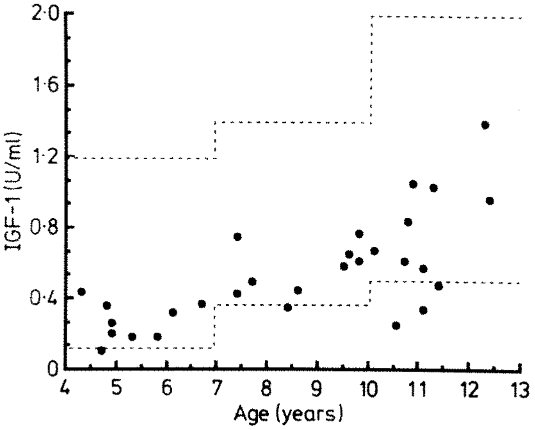


Fig 4 *Changes in plasma IGF-1 concentrations with age in 29 patients with Turner's syndrome. Lines indicate the range seen in normal children (2 SD).*

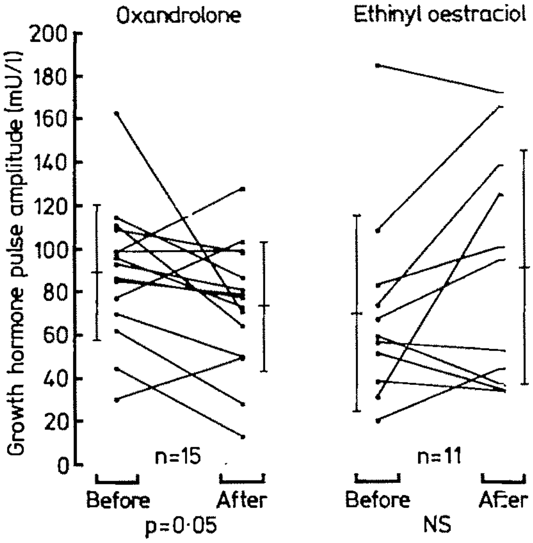


Fig 5 *Effects of oxandrolone and ethinyl oestradiol on the sum of growth hormone pulse amplitudes in 26 patients with Turner's syndrome. Bars indicate mean (SD).*

failed to reach significance (p>0·05). One of two abnormal pretreatment profiles became normal on ethinyl oestradiol. IGF-1 concentrations were unchanged.

Discussion

Growth in the middle childhood years is largely dependent on growth hormone and independent of sex steroids.[18] Analysis of 24 hour spontaneous growth hormone secretion in short prepubertal children has shown a gradual increase in growth hormone sum of pulse amplitudes over this age range and an asymptotic relation between the growth hormone sum of pulse amplitudes and height velocity SDS.[9]

In the only previous study of 24 hour growth hormone secretion in Turner's syndrome, Ross *et al* found a decline in both frequency and pulse amplitude after the age of 9 years.[19] Ranke *et al* recently reported a similar decline in amplitude of the maximum nocturnal pulse.[20] Our study suggests a steady decline in pulse amplitude over the mid childhood age range but no trend in pulse frequency. Comparison with data on normal short prepubertal subjects[21] shows similar concentrations of growth hormone sum of pulse amplitudes to 10 years of age with an increasing disparity as growth hormone secretion increases in normal children and decreases in Turner's syndrome.

The relevance of this decline is uncertain as the growth rates did not correlate with any measure of growth hormone secretion. In addition, those subjects with the lowest growth hormone secretion did not necessarily exhibit particularly poor growth. We have not attempted to use mean growth hormone concentrations; the data from growth hormone profiles do not approximate to a normal distribution and such an artificial smoothing of the data is unlikely to express the dynamics of a pulsatile system meaningfully.

Six of 35 patients (17%) had loss of the normal three hourly periodicity.[8] This is by way of contrast with our wider experience in which such abnormalities are very few and are associated with particularly poor growth.

IGF-1 concentrations were at the lower end of the normal range, but increased with age confirming previous studies,[5 11 19] although Cuttler *et al* were unable to find an increase after 10 years of age.[22] This increase occurred despite absent gonadal steroids and declining growth hormone secretion. IGF-1 concentrations did not correlate with height velocity SDS. (The strong negative correlation with

Table 2 *Effects of treatment with oxandrolone or ethinyl oestradiol*

	No of patients	*Pretreatment*	*Treatment*	*p Value*
	(a) Oxandrolone			
Height velocity SDS	11	0·0 (0·5)	2·5 (1·0)	<0·005
Growth hormone sum of pulse amplitudes (mU/l)	15	89·3 (31·6)	73·3 (29·7)	0·05
Growth hormone pulses per 24 hours	15	6·9 (2·4)	7·0 (1·9)	NS
IGF-1 (U/ml)	11	0·53 (0·21)	0·84 (0·37)	<0·05
	(b) Ethinyl oestradiol			
Height velocity SDS	11	0·1 (0·6)	1·8 (1·4)	<0·01
Growth hormone sum of pulse amplitudes (mU/l)	11	70·2 (45·4)	91·5 (54·0)	NS
Growth hormone pulses per 24 hours	11	6·8 (2·9)	6·7 (2·3)	NS
IGF-1 (U/ml)	6	0·70 (0·31)	0·90 (0·21)	NS

height velocity reflects their opposite age related trends.) The severe limitations of the measurements of circulating concentrations of such a paracrine hormone as IGF-1 have to be born in mind.[23] In this context, however, the data probably do exclude a failure of IGF-1 generation by growth hormone. Although Rosenfeld *et al* showed normal IGF-1 binding and action on fibroblast cultures,[24] actions on the growth plate are unknown.

The decline in growth hormone secretion could be ascribed to absence of gonadal steroids. Oestrogens in pharmacological doses have been shown to increase the growth hormone response to pharmacological stimuli in adults[25] and children[26] and the pubertal growth spurt in girls has been attributed to growth hormone secretion induced by oestrogens, though appropriate gonadotrophin secretion may also be necessary.[27]

In our study ethinyl oestradiol failed to have a consistent effect on growth hormone secretion, though it should be stressed that oral ethinyl oestradiol does not provide physiological oestrogen replacement. We used somewhat less than the 100 ng/kg dose that Ross *et al* found to induce the maximal short term growth response.[12] In our experience, such a dose commonly induces florid pubertal changes, which would not have been appropriate in the younger patients. A large dose of 100 μg of ethinyl oestradiol per day did increase growth hormone secretion in adult patients with Turner's syndrome.[28] It is of note that in castrate baboons, oestrogen treatment only increased growth hormone secretion if used in excessive amounts, 'replacement' doses having no effect.[29]

Oxandrolone produced a consistent improvement in growth without increasing the amplitude of growth hormone secretion. This has also been observed in boys with constitutional delay of growth and development.[30] We noted a qualitative improvement in pulse pattern in three patients. Time series analysis from three other patients showed that oxandrolone induced subtle changes in pulse frequency not apparent in the PULSAR analysis.[31] Oxandrolone increased IGF-1 as reported by others.[11]

In conclusion, although growth hormone secretion declined with age in Turner's syndrome, the relation to growth is uncertain, and end organ resistance in the form of a skeletal dysplasia probably plays a major part in the growth failure.[1–5] The experience that higher doses of growth hormone are required to achieve the same response as normal children supports this view and is against decreased bioactivity of endogenous growth hormone. Long term growth hormone treatment in pharmacological doses may nevertheless improve height prognosis. The onset of growth failure in early life implies that such treatment should be commenced well within the first decade. Our results suggest that tests of growth hormone secretion may not be helpful in selection of patients for such treatment. Oxandrolone and ethinyl oestradiol remain effective modes of treatment in Turner's syndrome, though their mechanisms of action in growth promotion remain uncertain.

Dr Massarano is supported by Action Research for the Crippled Child.

References

[1] Brook CGD, Murset G, Zachmann M, Prader A. Growth in children with 45,XO Turner's syndrome. *Arch Dis Child* 1974;**49:**789–95.

[2] Ranke MB, Pfluger H, Rosendahl W, *et al*. Turner syndrome: spontaneous growth in 150 cases and review of the literature. *Eur J Pediatr* 1983;**141:**81–8.

[3] Brook CGD. Growth hormone deficiency in Turner's syndrome. *N Engl J Med* 1978;**298:**1203–4.

[4] Kaplan SL, Abrams CAL, Bell JJ, Conte FA, Grumbach MM. Growth and growth hormone I: changes in serum level of growth hormone following hypoglycaemia in 134 children with growth retardation. *Pediatr Res* 1968;**2:**43–63.

[5] Morabito F, Caiazza F, Barreca A, *et al*. Human growth hormone, immunoreactive insulin and somatomedin activity in Turner's syndrome. In: Gedda L, Parisi P, eds. *Auxology: human growth in health and disorder*. London: Academic Press, 1978:261–8.

[6] Finkelstein JW, Roffwarg HP, Boyar RM, Kream J, Hellman L. Age-related change in the twenty-four-hour spontaneous secretion of growth hormone. *J Clin Endocrinol Metab* 1972;**35:**665–70.

[7] Spiliotis BE, August GP, Hung W, Sonis W, Mendelson W, Bercu BB. Growth hormone neurosecretory dysfunction: a treatable cause of short stature. *JAMA* 1984;**251:**2223–30.

[8] Albertsson-Wikland K. The effect of human growth hormone injection frequency on linear growth rate. *Acta Paediatr Scand* 1987;**Suppl 337:**110–6.

[9] Hindmarsh P, Smith PJ, Brook CGD, Matthews DR. The relationship between height velocity and growth hormone secretion in short prepubertal children. *Clin Endocrinol* 1987;**27:**581–91.

[10] Urban MD, Lee PA, Dorst JP, Plotnick LP, Migeon CJ. Oxandrolone therapy in patients with Turner syndrome. *J Pediatr* 1979;**94:**823–7.

[11] Rosenfeld RG, Hintz RL, Johanson AJ, *et al*. Methionyl human growth hormone and oxandrolone in Turner syndrome: preliminary results of a prospective randomized trial. *J Pediatr* 1986;**109:**936–43.

[12] Ross JL, Cassorla FG, Skerda MC, Valk IM, Loriaux DL, Cutler GB. A preliminary study of the effect of estrogen dose on growth in Turner's syndrome. *N Engl J Med* 1983;**309:**1104–6.

[13] Ross JL, Long LM, Skerda M, *et al*. Effect of low doses of estradiol on 6-month growth rates and predicted height in patients with Turner syndrome. *J Pediatr* 1986;**109:**950–3.

[14] Blethan SL, Chasalow FI. Use of a two-site immunoradiometric assay for growth hormone (GH) in identifying children with GH dependent growth failure. *J Clin Endocrinol Metab* 1983;**57:**1031–5.

[15] Merriam GR, Wachter KW. Algorithms for the study of episodic hormone secretion. *Am J Physiol* 1982;**243:**E310–8.

[16] Baxter RC, Brown SA, Turtle JR. Radioimmunoassay for somatomedin C: comparison with radioreceptor assay in patients with growth hormone disorders, hypothyroidism and renal failure. *Clin Chem* 1982;**28:**488–95.

[17] Tanner JM, Whitehouse RH, Cameron N, Marshall WA, Healy MJR, Goldstein H. *Assessment of skeletal maturation and prediction of adult height (TW2 method)*. New York: Academic Press, 1975.

[18] Karlberg J, Fryer JG, Engstrom I, Karlberg P. Analysis of linear growth using a mathematical model. II. From 3 to 21 years of age. *Acta Paediatr Scand* 1987;**Suppl 337:**12–29.

[19] Ross JL, Long LM, Loriaux DL, Cutler GB. Growth hormone secretory dynamics in Turner syndrome. *J Pediatr* 1985;**106:** 202–6.

[20] Ranke MB, Blum WF, Haug F, *et al.* Growth hormone, somatomedin levels and growth regulation in Turner's syndrome. *Acta Endocrinol* 1987;**116:**305–13.

[21] Hindmarsh PC, Matthews DR, Brook CGD. Growth hormone secretion in children determined by time sequence analysis. *Clin Endocrinol* 1988;**29:**35–44.

[22] Cuttler L, Van Vliet G, Conte FA, Kaplan SL, Grumbach MM. Somatomedin-C levels in children and adolescents with gonadal dysgenesis: differences from age-matched normal females and effect of chronic estrogen replacement therapy. *J Clin Endocrinol Metab* 1985;**60;**1087–92.

[23] Rosenfeld RG, Wilson DM, Lee PDK, Hintz RL. Insulin-like growth factors I and II in evaluation of growth retardation. *J Pediatr* 1986;**109:**428–33.

[24] Rosenfeld RG, Dollar LA, Hintz RL, Conover C. Normal somatomedin-C/insulin-like growth factor I binding and action in cultured human fibroblasts from Turner syndrome. *Acta Endocrinol* 1983;**104:**502–9.

[25] Merimee TJ, Fineberg SE. Studies of the sex based variation of human growth hormone secretion. *J Clin Endocrinol* 1971;**33:** 896–902.

[26] Moll GW, Rosenfield RL, Fang VS. Administration of low-dose estrogen rapidly and directly stimulates growth hormone production. *Am J Dis Child* 1986;**140:**124–7.

[27] Stanhope R, Pringle PJ, Brook CGD. The mechanism of the adolescent growth spurt induced by low dose pulsatile GnRH treatment. *Clin Endocrinol* 1988;**28:**83–91.

[28] Laczi F, Julesz J, Janaky T, Laszlo FA. Growth hormone reserve capacity in Turner's syndrome. *Horm Metab Res* 1979;**11:**664–6.

[29] Copeland KC, Johnson DM, Kuehl TJ, Castracane VD. Estrogen stimulates growth hormone and somatomedin-C in castrate and intact female baboons. *J Clin Endocrinol Metab* 1984;**58:**698–703.

[30] Link K, Blizzard RM, Evans WS, Kaiser DL, Parker MW, Rogol AD. The effect of androgens on the pulsatile release and the twenty-four-hour mean concentration of growth hormone in peripubertal males. *J Clin Endocrinol Metab* 1986;**62:**159–64.

[31] Hindmarsh PC, Stanhope R, Smith PJ, Pringle PJ, Brook CGD. Reproducibility of 24 hour growth hormone profiles in children. *J Endocrinol* 1986;**108**(suppl):Abstract 308.

Correspondence to Dr CGD Brook, Endocrine Unit, Middlesex Hospital, London W1N 8AA.

Accepted 10 October 1988

Archives of Disease in Childhood, 1989, **64**, 593–595

Thyroid dysfunction after radiotherapy and chemotherapy of brain tumours

E A LIVESEY AND C G D BROOK

Endocrine Unit, Middlesex Hospital, London

SUMMARY We investigated thyroid function in 119 survivors of treatment for brain tumours not involving the hypothalamo-pituitary region. Cranial irradiation did not effect thyroid function but 11 of 47 children (23%) who had spinal irradiation had raised concentrations of thyroid stimulating hormone. Chemotherapy further increased the incidence of thyroid dysfunction: two of four patients who had cranial irradiation and chemotherapy and 20 of 29 patients (69%) who had spinal irradiation and chemotherapy had increased thyroid stimulating hormone concentrations. Only six patients with raised thyroid stimulating hormone concentrations had low serum thyroxine concentrations. Four children had secondary hypothyroidism.

Thyroid function should be monitored in children who have received chemotherapy or radiotherapy. A rise in thyroid stimulating hormone concentrations is the most sensitive indicator of thyroid dysfunction. Children with raised thyroid stimulating hormone concentrations should be treated with thyroxine.

Endocrine complications of radiotherapy and chemotherapy given to children with brain tumours separated from the hypothalamo-pituitary axis have been documented.[1] Growth hormone insufficiency is the commonest disorder,[2] followed by primary thyroid and gonadal dysfunction, and then secondary thyroid and gonadal dysfunction.[3 4] Irradiation is the major aetiological factor, but chemotherapy has been found to cause primary gonadal damage.[5-7] There is only limited information from small studies about thyroid function and we report our observations on the prevalence, aetiology, and management of thyroid dysfunction in a large series of survivors.

Patients and methods

The thyroid function of 119 children in clinical remission after treatment of a brain tumour not involving the hypothalamo-pituitary region was studied. The tumour diagnoses were medulloblastoma (n=52), astrocytoma (n=29), ependymoma (n=15), pinealoblastoma (n=9), glioma (n=8), optic nerve glioma (n=5), and meningioma (n=1). Cranial irradiation in a median (range) estimated hypothalamic dose of 47 Gy (10–55) in 34 fractions (30–40) was given to all patients and 76 had also received spinal irradiation in a median spinal dose of 31 Gy (30–33) in 25 fractions (20–30) combined in 29 cases with chemotherapy. Four children received cranial irradiation and chemotherapy. The cytotoxic agents were lomustine, vincristine, and methotrexate alone or in varying combinations, usually following the schedules of the International Society of Paediatric Oncology.[8] The median total doses given were lomustine 550 mg/m^2 (320–1333), vincristine 36 mg/m^2 (5–51), and methotrexate 1·5 g/m^2 (0·1–4·5). The median age at the start of radiotherapy as 6·7 years (1·5–15) and median follow up after radiotherapy 8·5 years (1–27).

Serum total thyroxine and thyroid stimulating hormone (by immunoradiometric assay) concentrations were measured in all children at variable intervals after treatment (normal serum thyroid stimulating hormone concentration <4·8 mU/l, normal total serum thyroxine 60–140 nmol/l). Thyroid stimulating hormone concentrations were also measured by the Delfia method on the same samples in 38 patients for comparison and confirmation (normal thyroid stimulating hormone (Delfia) <3·8 mU/l).[9] Thyroid stimulating hormone responses to intravenous thyrotrophin releasing hormone 200 µg were documented in children undergoing investigation of the hypothalamo-pituitary axis because of poor growth. Thyroid autoantibodies were measured.

Primary thyroid dysfunction was defined as a raised basal serum concentration of thyroid stimulating hormone supported, if available, by an exaggerated response to thyrotrophin releasing hormone. Secondary hypothyroidism was diagnosed from a low serum thyroxine with low serum thyroid stimulating hormone concentration. Statistical analyses were performed using the Mann-Whitney and χ^2 tests.

Results

A total of 31 of 76 children (41%) treated with spinal irradiation had raised basal and peak serum thyroid stimulating hormone concentrations and six of these had low serum thyroxine concentrations (figure). The median basal thyroid stimulating hormone concentration in the affected group was 7·8 mU/l (5·0–39), the median peak thyroid stimulating hormone concentration after thyrotrophin releasing hormone was 37 mU/l (23–85), and the median serum thyroxine concentration was 76 nmol/l (10–118). Eleven of these children had received only radiotherapy; this was combined with chemotherapy in 20. As the table shows, there was a significant relation between primary thyroid dysfunction and spinal irradiation ($p<0·01$), which was expected, but the addition of chemotherapy to spinal irradiation resulted in a significantly increased incidence of thyroid dysfunction compared with that after spinal irradiation alone ($p<0·001$).

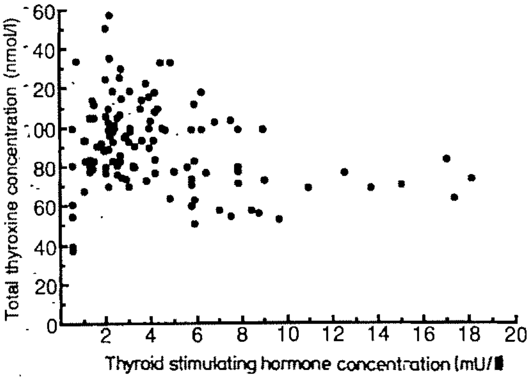


Figure *Serum thyroxine and thyroid stimulating hormone concentrations in 119 patients after treatment of brain tumours.*

Table *Treatment details of patients and primary thyroid dysfunction (n=119)*

	No of patients with thyroid dysfunction (total irradiated)	
	Without chemotherapy	*With chemotherapy*
Cranial irradiation (n=43)	0 (39)	2 (4)
Craniospinal irradiation (n=76)	11 (47)	20 (29)

The cytotoxic agents given to the affected group were lomustine plus vincristine in 19 children and vincristine alone in the other child. There were no significant differences in the doses or timing of cytotoxics, nor in age at treatment between affected and unaffected children. Raised and normal basal serum thyroid stimulating hormone concentrations were confirmed by the alternative Delfia method in the samples tested. No thyroid autoantibodies were detected in affected children.

Two of the four children treated with chemotherapy without spinal irradiation had raised serum thyroid stimulating hormone and low serum thyroxine concentrations (thyroid stimulating hormone 5·8/8·7 mU/l, thyroxine 60/56 nmol/l). Both had received lomustine alone (figure), but not all children treated with lomustine were affected. No child had abnormal thyroid function after cranial irradiation alone.

Four children had secondary hypothyroidism with a median serum thyroxine of 50 nmol/l (37–55), median thyroid stimulating hormone <1 mU/l.

Discussion

This is the largest study of thyroid function after treatment of brain tumours separated from the hypothalamo-pituitary area. The prevalence of primary thyroid dysfunction was 28% compared with 3% for secondary dysfunction. This reflects the expected association between spinal irradiation and primary thyroid dysfunction in this dose range and fractionation.[4 5 10–12] Unexpectedly, we found a significantly higher prevalence of primary thyroid dysfunction after treatment with a combination of chemotherapy and spinal irradiation than after spinal irradiation alone. This effect of chemotherapy has not been reported previously in children. Although the numbers were small, two children treated with cranial irradiation and chemotherapy were affected, which suggested that the toxic effects of chemotherapy may have been independent of those of radiotherapy.

Thyroid damage after treatment of brain tumours and lymphomas in childhood has previously been related to the local irradiation alone even though some of the affected children had also received chemotherapy. The numbers studied were too small to draw other conclusions.[5 11–13] Bajorunas *et al*, for example, described raised serum thyroid stimulating hormone concentrations in three of 12 children with head and neck tumours treated with chemotherapy and tumour irradiation, but only two of the three had received thyroid irradiation and the chemotherapy given to the third included carmustine and vincristine.[14] A relation between chemotherapy and subsequent primary thyroid dysfunction had been described earlier in 24 of 54 adults treated with chemotherapy alone for advanced Hodgkin's disease.[15] The cytotoxics were mustine, vincristine/vinblastine, procarbazine, and prednisolone in combination. In our study the combination of vincristine and lomustine with spinal irradiation obscured whether one or both cytotoxics was responsible for thyroid damage but there was some evidence for lomustine.

Most affected children in this series were biochemically euthyroid, as others have reported,[5,12] and an appreciable rise of serum thyroid stimulating hormone concentration was not often seen. If thyroid function had been monitored by measuring thyroxine concentrations alone, most of those affected would have been missed. The management of such children is unclear,[1] but patients with so called compensated thyroid dysfunction have been shown to have alterations in the cardiac systolic time interval that can be improved by thyroxine replacement.[16] There is also some evidence that a persistently raised serum thyroid stimulating hormone concentration increases the risk of thyroid cancer after thyroid irradiation.[17,18] It is not known whether correction of the thyroid stimulating hormone is protective. Our policy, and that of others,[1,5] is to monitor serum thyroid stimulating hormone concentrations annually after spinal irradiation or chemotherapy and to treat with thyroxine those in whom the thyroid stimulating hormone is raised.

The interval after treatment to the peak incidence of thyroid dysfunction is not known.[1] Ours was not a prospective study, but most abnormalities (24 of 33) were detected within four years of completing radiotherapy and three years of completing chemotherapy.

It has been suggested that post irradiation thyroid damage might be an autoimmune phenomenon. Tamura *et al* found an increased frequency of thyroid antibodies after neck irradiation in patients with lymphoma,[19] but we did not confirm this finding and the mechanism of the thyroid disturbance requires further study.

This study indicates a requirement to assess thyroid function in children who have received chemotherapy. It reinforces the need for lifelong surveillance of the endocrine function of patients treated with chemotherapy or radiotherapy in childhood.

We are grateful to Drs AC Whitton and J Britton and Professor RP Ekins for their help and to Drs N Godlee, J Tobias, and the late Professor HJG Bloom for access to their patient records. The study was supported by the Cancer Research Campaign.

References

[1] Shalet SM. Disorders of the endocrine system due to radiation and cytotoxic chemotherapy. *Clin Endocrinol* 1983;**18:**637–59.

[2] Shalet SM, Beardwell CG, Pearson D, Morris Jones PH. The effect of varying doses of cerebral irradiation on growth hormone production in childhood. *Clin Endocrinol* 1976;**5:** 287–90.

[3] Livesey EA, Brook CGD, Whitton AC, *et al.* Endocrine disorders following treatment of childhood brain tumours. *Int J Radiat Oncol Biol Phys* (in press).

[4] Shalet SM, Beardwell CG, MacFarlane IA, Morris Jones PH, Pearson D. Endocrine morbidity in adults treated with cerebral irradiation for brain tumours during childhood. *Acta Endocrinol* 1977;**84:**673–80.

[5] Brown IH, Lee TJ, Eden OB, Bullimore JA, Savage DCL. Growth and endocrine function after treatment for medulloblastoma. *Arch Dis Chld* 1983;**58:**722–7.

[6] Ahmed SR, Shalet SM, Campbell RHA, Deakin DP. Primary gonadal damage following treatment of brain tumours in childhood. *J Pediatr* 1983;**103:**562–5.

[7] Livesey EA, Brook CGD. Gonadal dysfunction after treatment of intracranial tumours. *Arch Dis Child* 1988;**63:**495–500.

[8] Bloom HJG, Thornton Jones H. Adjuvant chemotherapy for medulloblastoma: the multicentre controlled trial of the International Society of Paediatric Oncology (SIOP). *Proceedings of the 13th International Congress of Chemotherapy*. Vienna, 1983.

[9] Lövgren T, Hemmilä I, Pettersson K, Halonen P. Time-resolved fluorometry in immunoassays. In: Collins WP, ed. *Alternative immunoassays*. Chichester: Wiley, 1985:203–17.

[10] Broadbent VA, Barnes ND, Wheeler TK. Medulloblastoma in childhood: long term results of treatment. *Cancer* 1981;**48:** 26–30.

[11] Duffner PK, Cohen ME, Anderson SW, *et al.* Long-term effects of treatment on endocrine function in children with brain tumors. *Ann Neurol* 1983;**14:**528–32.

[12] Oberfield SE, Allan JC, Pollack J, New MI, Levine LS. Long term endocrine sequelae after treatment of medulloblastoma: a prospective study of growth and thyroid function. *J Pediatr* 1986;**108:**219–23.

[13] Shalet SM, Rosenstock JG, Beardwell CG, Pearson D, Morris Jones PH. Thyroid dysfunction following external irradiation for Hodgkin's disease in childhood. *Clin Radiol* 1977;**28:**511–5.

[14] Bajorunas DR, Ghavimi F, Jereb B, Sonerberg M. Endocrine sequelae of antineoplastic therapy in childhood head and neck malignancies. *J Clin Endocrinol Metab* 1980;**50:**329–35.

[15] Sutcliffe SB, Chapman R, Wrigley PFM. Cyclical combination chemotherapy and thyroid function in patients with advanced Hodgkins disease. *Med Pediatr Oncol* 1981;**9:**439–48.

[16] Ridway EC, Cooper DS, Walker H, Rodbard D, Maloof F. Peripheral responses to thyroid hormone before and after l-thyroxine therapy in patients with subclinical hypothyroidism. *J Clin Endocrinol Metab* 1981;**53:**1238–42.

[17] Doniach I. Effects, including carcinogenesis, of ^{131}I and X-rays on the thyroid of experimental animals. *Health Phys* 1963;**9:** 1357–62.

[18] Lindsay S, Sheline GE, Potter GD, Chaikoff IL. Induction of neoplasms in the thyroid gland of the rat by X-irradiation of the gland. *Cancer Res* 1961;**21:**9–16.

[19] Tamura K, Shimaoka K, Friedman M. Thyroid abnormalities associated with treatment of malignant lymphoma. *Cancer* 1981;**47:**2704–11.

Correspondence to Dr CGD Brook, Endocrine Unit, Middlesex Hospital, London W1N 8AA.

Accepted 21 October 1988

Archives of Disease in Childhood, 1989, **64**, 596–599

Sleeping body temperatures in 3–4 month old infants

M P WAILOO, S A PETERSEN,* H WHITTAKER, AND P GOODENOUGH

*Departments of Child Health and *Physiology, University of Leicester*

SUMMARY Rectal, skin, and ambient temperatures were continuously recorded overnight from 3–4 month old normal infants in their home cots under conditions of room temperature and wrapping chosen freely by parents. It was found that rectal temperature was above 37°C when infants were put down, but fell rapidly to 36·4°C within one and a half hours, then stabilised for a few hours before rising steadily. This pattern was tied more closely to the time of putting down than time of day. The extent and rate of temperature fall did not correlate with any feature of the thermal environment. We also found that skin temperature changed much less than rectal temperature over the night, and for the first two hours in the cot there was no relation between skin and rectal temperature. There is therefore a well organised, endogenous rhythm of temperature in 4 month old infants.

At some time during the first year of life, infants develop rhythmical changes in certain body functions based on a 24 hour cycle,[1] whereby activities are at a peak during daytime wakefulness and decline during nightime with sleep.[2] Body temperature, in line with other functions, tends to fall during the night and rise during the day to levels predetermined endogenously.[3 4] It is possible, however, that other factors in a home environment—for example, ambient temperature, quality of clothing, or infection—might influence body temperature to produce variation that might modify the normal circadian rhythm. Recently the findings of raised core temperature at necropsy in children who died suddenly[5] have led to suggestions of fatal hyperpyrexia during sleep,[6] although it is unlikely that postmortem findings accurately reflect the temperature state of live babies. We studied the pattern of core temperature during sleep in babies at the age of peak incidence of sudden deaths with relation to the home conditions that may significantly alter that pattern.

Subjects and methods

Information on a random sample of 98 normal, full term, singleton babies was collected at birth, and permission obtained from parents for the body temperature to be monitored for one night during sleep between the ages of 3–4 months. At this time each child was visited at home, weighed, skin fold thickness measured at the mid forearm region, and information obtained on feeding pattern and the recent health of the baby. Three thermistor probes were securely attached to the baby: (a) at the centre of the forehead; (b) on the abdomen 3 cm to the left of the umbilicus; and (c) into the rectum 5 cm from the anal margin. A fourth probe was fixed at the cot side to measure room temperature. All probes were connected to a battery powered Grant Squirrel Data Logger that was set to make recordings to the nearest 0·1°C at one minute intervals throughout the night from 2200 to 0700. Each probe was secured with sticking plaster to ensure good contact during body movement or bowel actions. Before use the probes and data loggers were tested for accuracy, firstly by placing them in water at known temperatures, and secondly by observing them on babies of similar age admitted to the ward.

The infants in the study were closely monitored during the night, both to check the security of the probes and to standardise readings against clinical thermometers at half hourly intervals. Parents were advised not to alter clothing, wrapping, and room heating practice, so that recording under normal conditions could be obtained.

Note was made of the number of quality of each item of clothing and wrapping, so that the thermal conductivity (tog value) could be calculated.[7]

A diary of the night's events was kept by parents recording the time the infant was put to bed, waking, crying, etc, and recordings commenced an hour or so before bedtime. All measurements were taken during December–March so that the widest variation in environmental and room temperatures would be obtained.

SUBJECTS

Of the 98 subjects recruited into the study 74 were eventually available for recording of body temperatures. Of the recordings made only those of at least eight hours duration showing no evidence of disturbance of the probes were selected for analysis; this gave 67 subjects with a full data set. The seven remaining subjects yielded only partial temperature records.

The subjects ranged in age from 9·5 to 19·5 weeks (standardised to a 40 week gestation) at the time of recording with a mean (SEM) age of 14·81 (0·25) weeks. Only seven infants were outside the range of 12 to 18 weeks. The mean (SEM) body weight at monitoring was 6265 (80)g (range 4520–8100 g) and the birth weight 3257 (50)g (range 2360–4340 g). They slept in cots in rooms whose minimum temperature ranged from 5·8°C to 22·4°C with a mean (SEM) of 13·95 (0·44)°C, and were clothed and wrapped to tog values ranging from 5·1 to 29·2 with a mean (SEM) of 14·7 (0·89). The factors influencing wrapping and parental choice of room temperature are the subject of a separate report.[8]

Results

RECTAL TEMPERATURE

The data logger recorded temperature to the nearest 0·1°C at one minute intervals. Data were reduced to a 15 minute average and plotted over the period of recording. All but three of the plots showed the same characteristics. The three oddities showed a rise of rectal temperature, occasionally up to 38·5°C, and were not included in the study, though as their number was so small their inclusion would not affect any conclusions reported here.

In the remaining 64 recordings rectal temperature was generally above 37°C before the infant was put down, and then fell rapidly within an hour of placing in the cot to stabilise at a value around 0·8°C lower. There were occasional further falls of 0·1–0·2°C. After around five hours the rectal temperature rose steadily at a slower rate than its fall. Fig 1 shows examples of individual temperature records. Although the pattern is similar the timing varies by up to three hours either way, depending on the time of putting down.

Combining data across individuals at fixed times of night would therefore tend to obscure the pattern of change, because the patterns are not precisely time locked. Accordingly the records were all time shifted to superimpose the one event that did appear phase locked to the pattern, namely putting down in the cot, producing a curve whose time axis is expressed relative to bedtime.

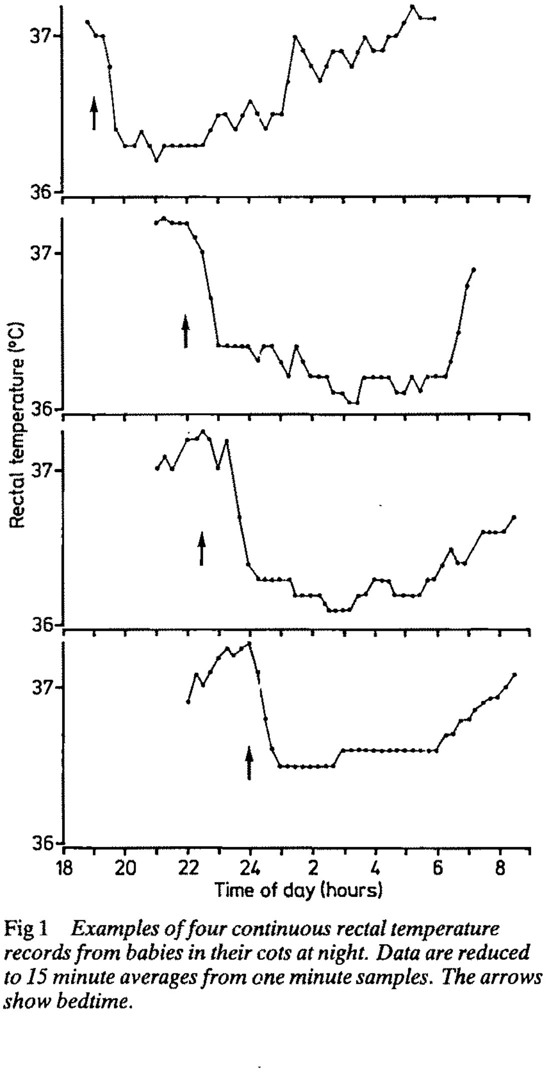


Fig 1 *Examples of four continuous rectal temperature records from babies in their cots at night. Data are reduced to 15 minute averages from one minute samples. The arrows show bedtime.*

Fig 2 shows the normalised data. On the assumption of a normal distribution of temperature, 90% of infants would be expected to fall in the range shown by the shading. Data do not depart significantly from a normal distribution. The distribution is not, however, wholly symmetrical, particularly during the period of stable rectal temperature two to five hours after putting the baby down (fig 3). Temperatures below 35·9°C were never recorded, yet temperatures above 37°C were not uncommon.

Ambient temperature fell at the same time as rectal temperature with a similar, though shallower, time course, showing a total fall of 4·4°C. The extent of the fall in rectal temperature in individuals did

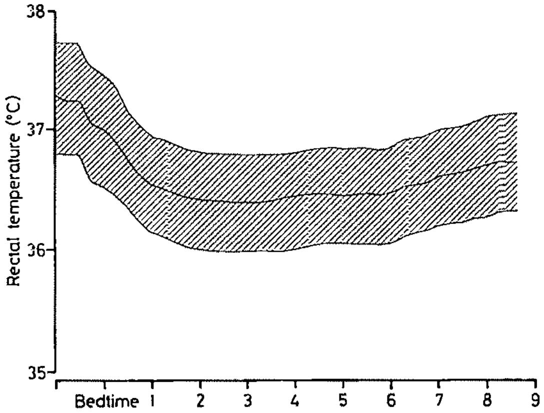


Fig 2 *Normalised curve for rectal temperature changes over time after bedtime. A total of 90% of infants would be expected to fall within the shaded area on the assumption of a normal distribution.*

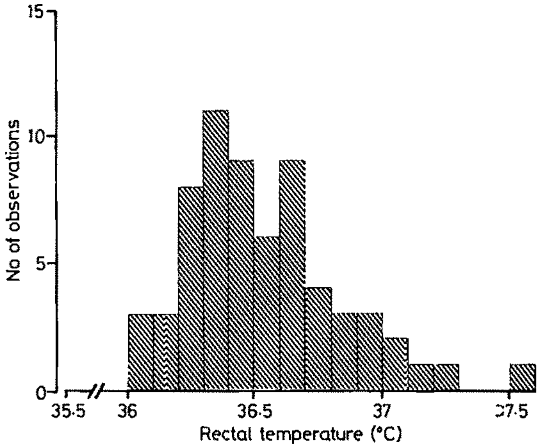


Fig 3 *Distribution of rectal temperatures across infants three hours after placing in their cot. Data do not depart significantly from a normal distribution but are slightly skewed to higher temperatures.*

not, however, correlate either with the minimum ambient temperature ($r=-0\cdot2$, $n=64$, $p>0\cdot05$) nor the fall in ambient temperature ($r=0\cdot05$, $n=64$, $p>0\cdot1$). Likewise, there was no correlation between rate of fall of rectal temperature and ambient temperature early in the night ($r=-0\cdot06$, $n=64$, $p>0\cdot1$).

The extent and rate of fall of rectal temperature also failed to correlate with the thermal insulation (tog value) of the infants' clothing and wrapping, so there is no evidence that the changes in rectal temperature are driven by the fall in ambient temperature.

SKIN TEMPERATURE

The temperature recorded by a thermistor on the skin of the abdomen did not reflect the pattern of rectal temperature. Fig 4 shows rectal and skin temperatures normalised to bedtime. Skin temperature was always lower than rectal, but varied much less over the night. The difference between skin and rectal temperature did, however, change appreciably.

The relation between skin and rectal temperature was examined by computing correlations between the two, both over successive measurements in the same individual, and over different individuals at the same time relative to bedtime. Over the whole night, fluctuation in abdominal skin and rectal temperature correlated significantly ($p<0\cdot05$) in only half of the children. There was a significant positive correlation in 19 (28%), and a significant negative correlation in 15 (22%). In the early part of the night rectal temperature was generally falling while skin temperature rose or remained stable, while late in the night both rose together. Which dominated determined the sign of the correlation if it existed. Restriction of the analysis to the final six hours of the recordings yielded significant positive correlations in 32 (48%) of subjects.

If data are correlated across individuals at constant time, then there is at most times a highly significant (usually $p<0\cdot001$) positive correlation with a slope close to 1. During the half hour before and the hour after putting down, however, there is no significant

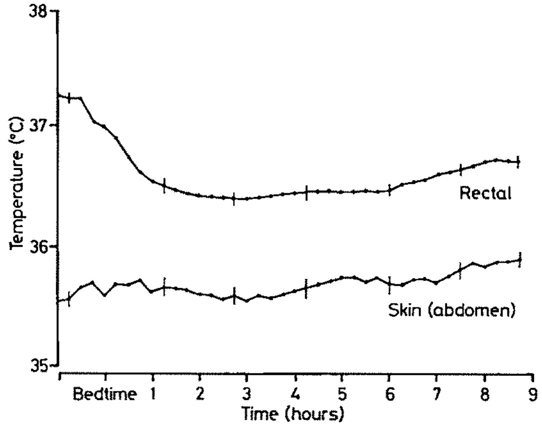


Fig 4 *Rectal and skin temperatures of infants over the night. Data are normalised to bedtime.*

correlation. Skin temperature therefore only reliably predicts rectal temperature once the infant has settled in its cot, and furthermore during the first hour after putting down the difference between skin and rectal temperatures decreases at the same rate as rectal temperature declines.

Discussion

Although circadian rhythms of body temperature were described early in this century,[1] there are few reports of continuous body temperature recordings in infants other than neonates,[2–4] and we can find no recordings made under home conditions. The data reported here describe rectal and skin temperatures during sleep in a good size sample of 4 month old babies, and allow an adequate description of normality for this group.

There is a very consistent pattern across individuals. All but three of the 74 subjects showed a fall in rectal temperature, which is phase locked to placing in their cot and presumably therefore falling asleep. The three oddities will be discussed in a separate report. While the fall clearly occurs at night, it is not a circadian rhythm precisely locked to time of day as some infants were put down as early as 1930 and achieved a low rectal temperature by 2030, whereas others were not put down until 0100, so their rectal temperature did not fall until 0230. It is for this reason that we have defined normality relative to the time of putting down, rather than time of night, although we are not denying the existence of circadian rhythmicity, as reported by previous authors.[1–4] It would be of great interest to discover what happens to rectal temperature during a sleeping period in day time.

Rectal temperature changes are only partly reflected by those of the skin. Up to two hours after putting to bed there is no relation between skin and rectal temperature either across or within individuals. This almost certainly reflects the impact of the greatly increased insulation provided by wrappings tending to inhibit skin cooling. Indeed, in some cases skin temperature rises appreciably. Later in the night skin and rectal temperature tend to change together, and each may be used to predict the other.

The phases of temperature change: rapid fall, stability, and slow rise are clearly part of a well orchestrated pattern, keeping temperature within narrowly defined limits irrespective of ambient temperature and insulation, suggesting that they are both internally driven and controlled. This should be taken into account when making clinical judgments based on spot temperature measurements taken during the night. Just before putting a baby down a temperature at the bottom end of the 'normal range' (36·2°C −37·2°C) is very unlikely, whereas two hours later a reading at the top end of the range is equally unlikely.

This study has therefore allowed a full description of the normal pattern of temperatures in 4 month old babies. Such a pattern is not apparent at birth, so we must now investigate when it develops and what factors influence its first appearance.

This work was supported by the Foundation for the Study of Infant Deaths.

References

[1] Minors DS, Waterhouse JM. Development of circadian rhythms in infancy. In: Davies JA, Dobbing J, eds. *Scientific foundations of paediatrics*. London: Heinemann, 1982:980–97.

[2] Hellbrügge T. The development of circadian rhythms in infancy. *Cold Spring Harbor Symposium on Quantitative Biology* 1960; **25**:311–23.

[3] Hellbrügge T, Lange J, Rutenfranz J, Stehr K. Circadian periodicity of physiological functions in difference stages of infancy and childhood. *Ann NY Acad Sci* 1964;**117**:361–73.

[4] Mills JN. Development of circadian rhythms in infancy. *Chronbiologia* 1975;**2**:363–71.

[5] Emery JL, Sunderland R. Febrile convulsions and cot death. *Lancet* 1981;**ii**:176–8.

[6] Stanton AN. Overheating and cot death. *Lancet* 1984;**ii**:1199.

[7] Clulow E. Thermal insulation properties of fabrics. *Textiles* 1978;**7**:2.

[8] Wailoo MP, Petersen SA, Whittaker H, Goodenough P. The thermal environment in which 4 month old infants sleep at home. *Arch Dis Child* 1989;**64**:600–4.

Correspondence to Dr MP Wailoo, Department of Child Health, University of Leicester, PO Box 138, Leicester LE1 9HN.

Accepted 6 October 1988

Archives of Disease in Childhood, 1989, **64,** 600–604

The thermal environment in which 3–4 month old infants sleep at home

M P WAILOO, S A PETERSEN,* H WHITTAKER, AND P GOODENOUGH

*Departments of Child Health and *Physiology, University of Leicester*

SUMMARY The thermal insulation of clothing and wrapping (tog value), room temperature, and body temperature was measured for 3–4 month old infants sleeping in their home cots under conditions chosen freely by parents during a cold winter. We found that ambient temperature averaged 18·4°C when infants were put down, but fell by an average of 4·4°C during the night. Minimum room temperature correlated with outside temperature, but most rooms were heated to some degree; smaller babies were kept in warmer rooms. The tog value of clothing before putting the baby down averaged 5·1, supplemented by 9·6 tog units of wrapping in the cot—a 188% increase for a 4·4°C drop in temperature.

Total tog of clothing and wrapping correlated negatively with minimum room temperature; smaller born babies tended to be more heavily wrapped. Despite the large increase in insulation in the cot, most babies maintained normal body temperatures.

Over the last couple of decades there has been a substantial increase in the variety of items for clothing and wrapping of babies, and a rise in the number of homes with central heating. There are few reports, however, of the thermal consequences of the way in which parents now clothe and wrap their babies.[1]

Recent reports of raised core temperature in some sudden infant deaths,[2] and subsequent retrospective analysis of clothing and wrapping,[3] have suggested that 'over wrapping' may be a contributory factor, but is not clear how 'over wrapping' can be defined as we have no precise information about either the range of normal parental behaviour or how it affects infant thermoregulation.

In this study we report data on the room temperatures to which normal 4 month old infants were exposed at home during the night, the extent to which they were clothed and wrapped, and the factors that parents took into account in deciding the appropriate combination of room heating and coverings for sleeping babies during a cold British winter.

Subjects and methods

Information on a random sample of normal, full term, singleton babies was collected at birth, and permission obtained from parents for the body temperature to be monitored for one night during sleep between the ages of 3–4 months. At this time each child was visited at home, weighed, skin fold thickness measured, and information obtained on feeding pattern and the recent health of the baby. Three thermistor probes were securely attached to the baby: (a) at the centre of the forehead; (b) on the abdomen 3 cm to the left of the umbilicus; and (c) into the rectum 5 cm from the anal margin. A fourth probe was fixed at the cot side to measure room temperature. All probes were connected to a Grant Squirrel Data Logger that was set to make recordings at one minute intervals throughout the night from 2200 to 0700.

Parents were advised not to alter clothing, wrapping, and room heating practice, so that recording of normal conditions could be obtained.

The researchers noted the number and quality of each item of clothing and wrapping, and the thermal conductivity (tog value) calculated using the standard set at the Shirley Institute, Manchester[4] and from data provided by Clulow (E Clulow, personal communication) (table). For each baby a total tog value for clothing and wrapping was obtained, which could be related to the changes in body temperature. If wrappings were folded, allowance was made in the calculations. One tog unit is the thermal resistance of a fabric when the temperature difference between its faces is 0·1°C for a flow of heat equivalent to one watt per square metre.

Table *Standard tog values used to quantify the insulation on sleeping babies. Data supplied by the Shirley Institute, Manchester (E Clulow, personal communication)*

Garment or wrapping	*Tog value*
Vest	0·2
Babygro	1
Winter dress or pyjamas	2
Jumper, trousers	2
Cardigan	2
Nappy (disposable)	2 (less when very wet)
Sleeping suit	4
Baby Nest	4
Sheet	0·2
Old blanket	1·5
New blanket	2·0
Quilts	Manufacturers' figures: typically 9

A diary of the night's events was kept by the parents and recorded the time the baby was put to bed and any episodes of waking, crying, etc; the recordings commenced at bedtime. In all cases infants remained in the same clothing and wrapping throughout the recording period, with the occasional exception of a nappy change. All measurements were taken during December–March so that the widest variations in environmental and room temperatures would be obtained.

After monitoring, the computerised data on each baby was extracted to show a minute by minute record of all temperatures simultaneously, and scrutinised for inaccuracies or artefacts. Only unblemished recordings were analysed.

SUBJECTS

A total of 98 subjects were recruited to the study, but full recordings were made on only 74, as some infants were ill or unavailable at the proposed time of recording.

The subjects ranged in age from 9·5 to 19·5 weeks (standardised to a 40 week gestation) at the time of recording with a mean (SEM) of 14·81 (0·25) weeks. Only seven infants were outside the range of 12 to 18 weeks. The mean (SEM) body weight at monitoring was 6265 (80)g (range 4520–8100 g) and the birth weight 3257 (50)g (range 2360–4340 g). Mean (SEM) skin fold thickness at the time of recording was 10·58 (0·29) mm. Some infants suffered mild infections during the week before recording, but none were ill on the day, or became so within two days.

Results

ROOM TEMPERATURES

Of the 74 homes studied, 41 (55%) had central heating, 26 (35%) local heating in the bedroom, and seven (10%) no heating in the bedroom. A total of 19 (26%) kept the heating on all night and 45 (61%) part of the night, usually the late evening and early morning; the remainder provided no heat to the bedroom during the time of recording.

When the babies were put down, the mean (SEM) ambient temperature was 18·43 (0·42)°C. Fig 1 shows the changes over the following eight hours. Data were normalised to the time of putting down in order to maintain compatibility with measurements of rectal and skin temperature reported elsewhere.[5] Bedtime ranged from 1800 to 0100, with a median of 2115. In almost all cases, however, the rooms were heated until the baby was put down, and only then allowed to cool, so the normalisation procedure does accurately reflect the ambient temperature to which babies are exposed in various states of sleep or wakefulness.

By six hours after putting down, mean (SEM) ambient temperature had fallen to 14·0 (0·63)°C,

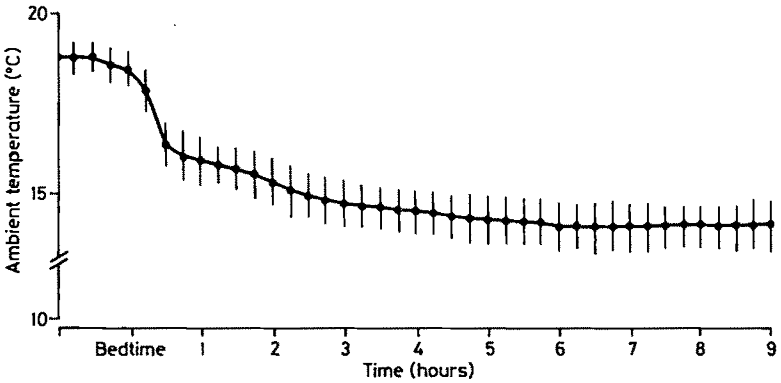


Fig 1 *Mean (SEM) ambient temperature of the babies' bedrooms over winter nights.*

but this mean disguised a considerable increase in range. In some cases temperature fell to below 7°C, in others it stayed above 22°C. Fig 2 shows the distribution of ambient temperature just before and six hours after putting down.

Minimum room temperature correlated positively with minimum outside temperature (r=0·31, p<0·01, n=74). The minimum outside temperature ranged from −9 to +6°C, with a mean of −0·2°C. At any given outside temperature, ambient temperature could range over many degrees. Other factors, including room heating, were significant.

Minimum room temperature correlated negatively with the weight of the infant at monitoring (r=−0·31, p<0·01, n=74), but did not correlate with age or skin fold thickness. Only 24 (32%) babies below median body weight were in rooms where temperature fell below median minimum (χ^2=9·14, with 1 df, p<0·01). There was also a significant negative correlation between minimum temperature and birth weight (r=−0·22, p<0·05, n=74).

Smaller babies therefore slept in warmer rooms.

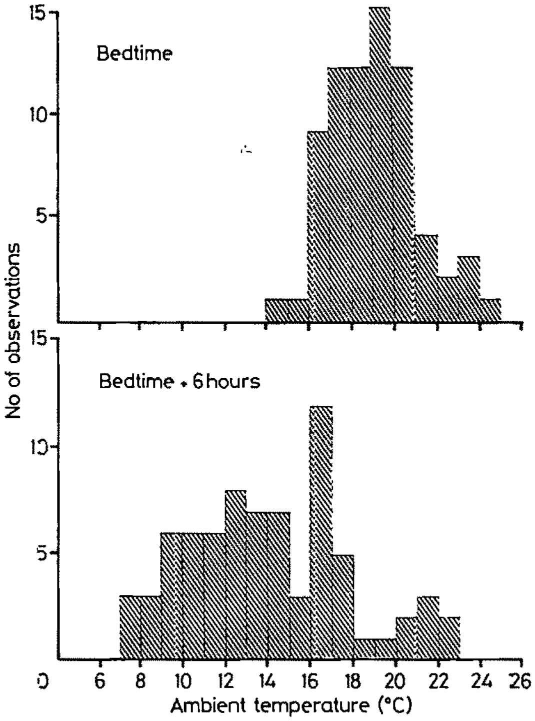


Fig 2 *Distribution of ambient temperature in the babies' bedrooms just before they were put down and six hours later.*

CLOTHING AND WRAPPING

The mean tog value of clothing worn before putting down was 5·1 with a range of 2·4 to 10·2. When placed in the cot, babies were wrapped, on average, with an additional 9·6 tog units (range 1·9 to 19·3). A 4·4°C drop in ambient temperature was therefore associated with a 188% increase in insulation, not taking into account the insulation afforded by a foam mattress.

Tog value of clothing and wrapping taken together correlated negatively with the minimum ambient temperature (r=−0·36, p<0·01, n=74) (fig 3), but did not correlate with room temperature at bedtime. Around 12% of parents seemed to apply much more wrapping than the others (see fig 3). There was a weak positive correlation between total tog value and body weight at monitoring (r=0·21, p<0·15, n=74), but a weak negative correlation between total tog value and birth weight (r=−0·16, p<0·1, n=74). While there was not a strong linear relation between body and birth weight and total tog value it was clear that lower birthweight babies were more heavily insulated. Only 24 (32%) of the babies above median birth weight had wrapping with tog values above median.

Tog value was, therefore, related to the minimum ambient temperature in the room, but this relation was modified to some degree by the birth weight of the baby.

Discussion

We have examined the conditions under which normal 4 month old infants sleep at home during a cold spell of a British winter. The data were collected as part of a larger study and appeared to parents as incidental to the main purpose of the investigation. Parents were also asked not to change their habits, and we have no evidence that they did, so we must assume that we are seeing normal parental behaviour.

In almost all cases, the infants' rooms were heated during the evening, so that at bedtime room temperatures fell within a narrow range, despite a considerable range of outside temperatures. During the study minimum outside air temperature ranged from −9 to +6°C.

In most cases room temperature then fell during the night; the extent of fall, though related to outside temperature, was not great. The fall appeared to be attenuated or prevented to a variable degree by room heating so that overall temperature fell, on average, by only 4·4°C.

The minimum room temperature reached during the night correlated negatively with the body weight and birth weight of the babies, suggesting that

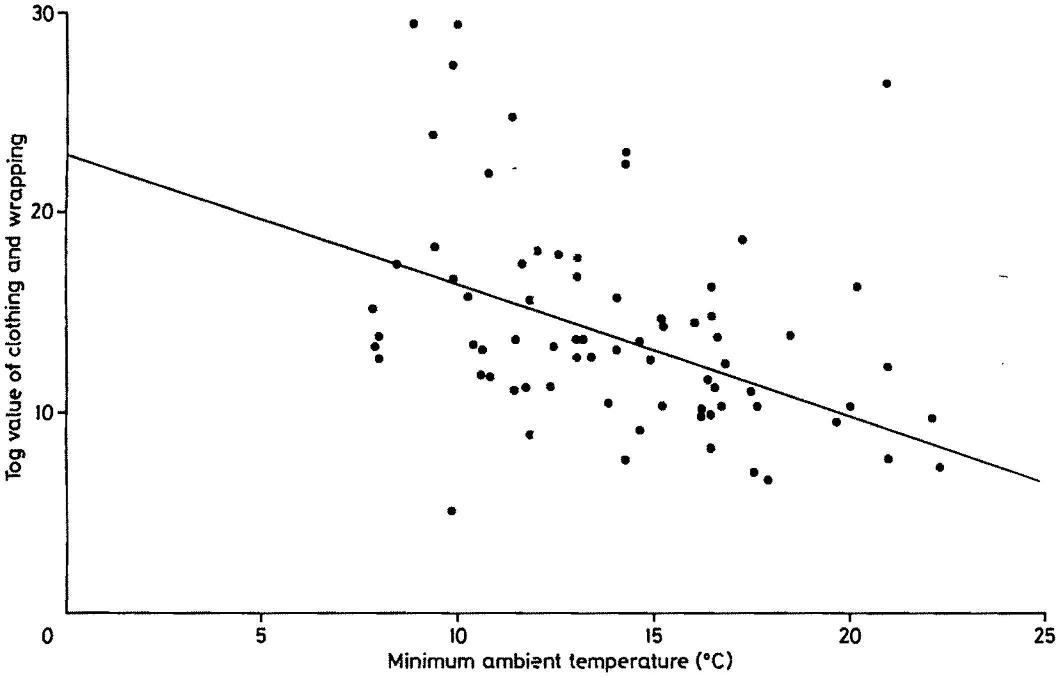


Fig 3 *Relation between the combined tog value of clothes and wrappings and minimum ambient temperature in the babies' bedrooms.*

parents are more likely to provide night time heating for smaller babies.

When infants are put down they are wrapped with considerable extra thermal insulation, which rises by 188%. Parents are presumably guarding against potential falls in body temperature. While the rooms do cool, they do not do so immediately, most reaching their minima after many hours, and in any case the overall fall in temperature is not great. Even allowing for an assumed drop of 30–40% or so in metabolic rate during sleep it is difficult to see the need for such a dramatic increase in insulation. Either infants are under insulated before putting down, or over insulated after, particularly during the first few hours of the night. Indeed Clulow (E Clulow, personal communication) has calculated, using the formula of Barton and Edholm,[6] that the appropriate tog value for the insulation of a sleeping baby at 16°C should be 8·8. The same formula yields a prediction of 10·5 tog for 14°C. As we report elsewhere,[5] however, most infants do appear capable of thermoregulation, and show a precisely controlled sequence of body temperature changes during the night.

The parental decision about clothing and wrapping is not a random one. Total thermal insulation is related to the minimum ambient temperature in the room, except for a small proportion of parents (12%) who wrapped much more heavily than others. Only one baby in the sample was much more lightly insulated than usual. Birth weight, though not age or current body weight, of the infants also appeared to exert a small influence on the extent of wrapping, in that at any given temperature smaller born babies appeared to be more heavily insulated.

Parents seem, therefore, to be working to a rough 'formula' relating insulation to perceived risk of hypothermia, taking into account how much the room temperature is expected to fall, and the vulnerability of the infant to that fall.

Two questions are immediately apparent. First, how is this formula established and second is it 'right' in the sense that it places infants in a thermal environment offering the least challenge to thermoregulation?

Parents receive advice on wrapping babies from a number of sources, other parents and health care workers being most obvious. We have no evidence that this advice is based upon objective estimates of what is best for babies, and in any case it is given mainly at the time of birth, and may set parental habits that become less appropriate as babies get older. There are recommendations about room temperature for babies, but these do not appear to be tied to similar recommendations about the thermal insulation that should be used.

It is clear that most babies can thermoregulate in their cots, though they may have to work quite hard to keep the temperature down. Many seem to sweat, and as we report elsewhere, skin temperature is relatively high, suggesting some peripheral vasodilatation.[5] This is particularly obvious from the head temperatures, which suggest that some 85% of the heat loss from the baby is via the head. This will be examined in detail in another report. It is just possible that some vulnerable babies may not rise as effectively to the thermal challenge as others, and indeed in three babies who we studied, and who were well, body temperature rose after a while in the cot, and eventually reached levels well above the top end of the normal range.

It is clear that more work is needed to establish how parents decide the thermal environment of their babies, and that there is a need for some relatively objective statement about which combination of wrapping and room temperature is most appropriate.

This work was supported by the Foundation for the Study of Infant Deaths.

References

[1] Nicholl A, Davies L. How warm are babies kept at home? *Health Visitor* 1986;**59**:113–4.

[2] Emery JL, Sunderland R. Febrile convulsions and cot death. *Lancet* 1981;**ii**:176–8.

[3] Stanton AN. Overheating and cot death. *Lancet* 1984;**ii**:1199.

[4] Clulow E. Thermal insulating properties of fabrics. *Textiles* 1978;**1**:2.

[5] Wailoo MP, Petersen SA, Whittaker H, Goodenough P. Sleeping body temperatures in 3–4 month old infants. *Arch Dis Child* 1989;**64**:596–9.

[6] Barton AC, Edholm OG. *Man in a cold climate*. London: Edward Arnold 1955.

Correspondence to Dr MP Wailoo, Department of Child Health, University of Leicester, PO Box 65, Leicester LE2 7LX.

Accepted 6 October 1988

Archives of Disease in Childhood, 1989, **64**, 605–609

Skin colour and bilirubin in neonates

A KNUDSEN AND R BRODERSEN

Department of Obstetrics and Gynaecology, County Hospital, Hjørring and Institute of Medical Biochemistry, University of Aarhus, Denmark

SUMMARY The correlation between the yellow colour of the skin and serum bilirubin concentration, reserve albumin concentration, and pH was investigated in 76 icteric neonates. Significant linear correlation existed between yellow colour of the skin and serum bilirubin concentration, reciprocal of the reserve albumin concentration, and the squared hydrogen ion concentration. Furthermore, the basic yellowness of the skin at birth correlated linearily with the yellow colour of the skin measured when the child became jaundiced.

The results support the proposed hypothesis that bilirubin is transferred from plasma to skin through two different mechanisms: (a) leakage of bilirubin-albumin complexes into extravascular spaces and (b) precipitation of bilirubin acid in phospholipid membranes. The latter mechanism suggests that measurement of the yellow colour of the skin may be a better predictor of brain damage than the serum bilirubin concentration and thus be of clinical utility. Measurement of the yellow colour of the skin as a method of obtaining serum bilirubin concentration is unreliable.

Measurement of the yellow colour of the skin, so called transcutaneous bilirubinometry, has been introduced as an alternative to determination of bilirubin in serum of neonates.[1 2] Several authors have found a good correlation between the instrument reading and the serum bilirubin concentration.[1–4] Even though a non-invasive method offers several advantages over an invasive procedure widespread use of the bilirubinometer has not been seen.[5] It may be noted in this connection that the reliability of serum bilirubin concentration as a risk indicator of bilirubin encephalopathy is questioned from different quarters.[6 7] Also, other factors than serum bilirubin concentration influence the readings.

The present investigation was undertaken in order to elucidate the meaning of measurements of the yellow colour of the skin, after consideration of possible bilirubin transfer mechanisms between blood plasma and skin tissue. The clinical utility of the method will be discussed in the light of the results obtained.

We hypothesise that bilirubin may be transferred to the skin through two different mechanisms: (a) by leakage of bilirubin-albumin from plasma into extravascular spaces and (b) by precipitation of bilirubin acid in phospholipid membranes.

The first of these two possibilities is an obvious one. A considerable amount of serum albumin is found outside the blood stream, the extravascular albumin pool constituting about 60% of the total in adults.[8] As bilirubin is bound with high affinity to albumin and as the intravascular and extravascular pools of the protein exchange, albeit slowly,[9] it can be presumed that the extravascular albumin becomes loaded with bilirubin. The skin contains considerable amounts of albumin. It is conceivable, therefore, that in the case of hyperbilirubinemia the skin will assume a yellow colour due to its content of bilirubin-albumin.

The second mechanism hypothesised above, precipitation of bilirubin acid, is likely to be active in icteric infants. It has been found that blood plasma in such cases is supersaturated with bilirubin acid,[10] and experiments in vitro have shown that the pigment promptly precipitates in phospholipid membranes when these are in contact with a supersaturated bilirubin solution.[11]

Other mechanisms appear unlikely at our present state of knowledge. The possibility that bilirubin should bind to collagen or elastin has been investigated and gave negative results (R Brodersen, unpublished observations). Likewise, dissolution of bilirubin in fat of adipose tissue has not been shown and seems remote after experiments in vitro as well as in vivo.[12 13]

If bilirubin in the skin tissue is present as bilirubin-albumin, then the yellow colour of the skin will be correlated to the plasma bilirubin concentration. If deposition of bilirubin acid is involved we further expect a negative correlation to the concentration of reserve albumin for binding of bilirubin and a negative correlation to plasma pH. It is the aim of the present paper to investigate whether such correlations exist and to discuss the possible bearing of these on bilirubin transfer mechanisms to the skin as well as to other tissues.

Theory

If the plasma concentration of bilirubin-albumin is B, and the first order rate constant for transfer of this complex to extravascular spaces in the skin is k_{p+} then the rate of transfer of bilirubin-albumin is Bk_{p+}. The rate of the reverse process, transfer of bilirubin-albumin from skin to plasma is then $B'k_p$, the bilirubin-albumin concentration in the extravascular spaces multiplied by the rate constant for the reverse transport. Deposition of bilirubin acid occurs through the process:

$$AB^{2-}+2H^+ \rightleftarrows BH_2+A \qquad (1)$$

The bilirubin-albumin complex, in which bilirubin is present as the dianion, combines with two hydrogen ions in the plasma and deposits a molecule of solid bilirubin acid in the capillary wall; one molecule of albumin without bilirubin is released and remains in the blood stream. The rate of bilirubin transfer through this process may be proportional to the concentration of bilirubin-albumin, B, and to the squared hydrogen concentration and can thus be expressed as $B10^{-2pH}k_{A+}$, when the rate constant is k_{A+} and as the hydrogen ion concentration is 10^{-pH}.

The reverse process, dissolution of bilirubin acid by reaction with albumin, takes place with release of two hydrogen ions and formation of one molecule of the bilirubin-albumin complex in the plasma. The rate of this process is presumably $aB''k_{A-}$, proportional to the reserve albumin concentration for binding of bilirubin, a. The amount of bilirubin acid per volume of skin tissue is B''. (We have disregarded the fact that albumin can bind more than one bilirubin dianion per molecule of the protein. Consideration of multiple bilirubin binding results in a more complicated deduction but the same final expression for the transfer rate, when a is used for the reserve albumin concentration, as previously defined.[14])

The net rate of bilirubin deposition in the skin is further influenced by elimination of bilirubin after photoisomerisation and possibly also by oxidation with bilirubin oxidase.[15] Let us denote the rates of these two processes by v_L and v_{0x} respectively. The rate of bilirubin deposition in the skin is then:

$$V=Bk_{p+}-B'k_{p-}+B10^{-2pH}k_{A+}-aB''k_{A-}-v_L-v_{0x} \qquad (2)$$

The intensity of the yellow colour of the skin at a given point of time, t_1, is considered to consist of a constant basic colour intensity, Y_0, which was present at the time of birth, t_0, and a contribution accumulated over the time. The total colour intensity is then:

$$Y=Y_0+\int_{t_0}^{t_1} V dt \qquad (3)$$

Equation (3) cannot be solved numerically in general terms, but an understanding of the dynamics involved may be obtained as follows. If jaundice is in an early phase of building up, we may consider B and pH approximately constant with time and B', B'', v_L and v_{0x} as zero, and obtain:

$$Y=Y_0+B\left(k_{P+}+10^{-2pH}k_{A+}\right)(t_1-t_0) \qquad (4)$$

In an early phase of jaundice we may thus expect to see the colour intensity of the skin increase linearly with time. If our hypothesised mechanisms of bilirubin transfer are correct we should observe that the colour intensity of the skin is positively correlated to the plasma bilirubin concentration, B, and negatively correlated to plasma pH.

Later on, as bilirubin accumulates in the tissue, the rates of reverse transport of bilirubin-albumin and of bilirubin acid dissolution increase. Also the rates of photoelimination and of bilirubin oxidation may become significant. A maximum level of jaundice may be reached, in healthy infants usually around the fourth day of life. The maximal colour intensity will depend upon the initial rate of colour increase and further be inversely related to the rate of bilirubin acid dissolution. If our hypothesis is correct, the maximal level of jaundice should therefore be positively correlated to the plasma bilirubin concentration and negatively to the plasma pH. A high reserve albumin concentration, a, will at this stage cause an increase of bilirubin acid dissolution and thus tend to decrease the maximal level.

An equilibrium may be established if the velocities of photoelimination and of enzymatic oxidation remain insignificant. In this case both the transport of bilirubin-albumin and the deposition of bilirubin acid will be in equilibrium, with equal rates of transport in and out of the tissue, We then have:

$$Bk_{p+}=B'k_{p-} \text{ and } B10^{-2pH}k_{A+}=aB''k_{A-} \qquad (5)$$

The skin colour consists of the basic colour, the bilirubin-albumin, and the bilirubin acid present in the tissue:

$$Y=Y_0+B'+B'' \tag{6}$$

B′ and B″ are isolated from equation (5) and entered into equation (6).

$$Y=Y_0+B\left(\frac{k_{P+}}{k_{P-}}+\frac{10^{-2pH}k_{A+}}{ak_{A-}}\right) \tag{7}$$

If our hypothesis is correct we expect, in a state of equilibrium between plasma and skin, to observe that the colour intensity of the skin is linearily related to the plasma bilirubin concentration, B, and further linearily related to the squared hydrogen ion concentration, 10^{-2pH}, and finally to the reciprocal of the reserve albumin concentration, 1/a.

In summary, the intensity of the yellow colour of the skin should be positively correlated to three indices: the plasma bilirubin concentration, the squared hydrogen ion concentration, and the reciprocal of the reserve albumin concentration. This should form a suitable basis for testing the hypothesis. It is obvious, however, that strict correlations to these indices cannot be expected. As seen from equations (4) and (7), the yellow colour varies with several factors, to different degrees under different circumstances. Weak correlations, if significant, must be accepted as positive findings.

Subjects and methods

The study population consisted of 76 healthy newborn babies admitted to the newborn nursery of Hjørring hospital. All infants were of more then 36 weeks' gestation. None of the infants suffered from haemolytic anaemia or had mothers who suffered from diabetes. No infants had been exposed to phototherapy or exchange transfusion before measurement. All measurements were obtained during the first five days after birth.

The readings of the yellow colour of the skin were taken with the Air Shields Jaundice Meter (Minolta Camera Co). The Air Shields Jaundice Meter is a hand held instrument that employs fibre optic techniques to illuminate the skin and subcutaneous tissue and then spectrophotometrically analyses the intensity of the yellow colour. The meter was used and tested daily as recommended by the manufacturer.[16]

All infants within the study period who had visible jaundice were included after informed consent. A single set of data was obtained from each infant at the time when the child was initially observed to be icteric. At the time of blood sampling for serum bilirubin concentration determination two meter readings were obtained from the forehead, which was the site chosen because of convenience and accessibility. Furthermore, the cephalocaudal progression of neonatal jaundice with higher bilirubin values could lead to some reservations being held on the reliability of the more distal sites for meter readings.[17] The average value of the two readings was obtained. The meter readings were performed by members of the nursing staff.

During a part of the study jaundice meter readings were obtained in all infants immediately after birth.

Blood samples were obtained by heel prick. The total bilirubin concentration was determined in capillary blood serum by a standard diazo method.[18] As all neonates in the study were mature, between 2 and 5 days old, icteric, but otherwise clinically well without diseases in the biliary system or infection, the amount of conjugated bilirubin in the blood was probably around 1% of the total serum bilirubin concentration.[19] Therefore, in the theoretical section, the concentration of conjugated bilirubin in serum was regarded as zero and the concentration of unconjugated bilirubin in serum was considered equal to the total serum bilirubin concentration. The reserve albumin concentration was measured using the ^{14}C-MADDS (monoacetyldiamino-diphenylsulphone) method.[14] pH was determined by an ABL3 pH/blood-gas analyser (Radiometer).

Results and conclusions

The meter readings ranged from 10 to 23 with mean (SD) value of 16 (2·6). The mean serum bilirubin concentration for all infants was 185 (47) μmol/l (range 68–282 μmol/l). The mean reserve albumin concentration was 129 (32) μmol/l (range 71–212 μmol/l). Plasma pH ranged from 7·30 to 7·48. The mean value was 7·40 (0·04).

Results of linear correlation analysis by the method of least squares are presented in the table. The correlation between serum bilirubin concentration and the yellow colour of the skin is pictured in the figure.

The yellow colour of the skin of icteric infants is thus correlated to the serum bilirubin concentration and inversely to the reserve albumin and pH, and further to the basic colour intensity measured at birth.

During the icterometer reading the skin is compressed so that blood is removed from the capillaries. The yellow colour is due to bilirubin located extravascularly in the skin, and to some extent to the basic colour of the tissue. The correlation of the colour intensity with serum bilirubin concentration

Table *Results of linear correlation analysis*

Correlation	*Coefficient of correlation*	*p Value*
Y *v* B	0·83	<0·0001
Y *v* 1/a	0·43	<0·001
Y *v* 10^{-2pH}	0·33	<0·02
Y *v* Y_0	0·35	<0·05
B *v* a	0·02	NS
B *v* pH	−0·12	NS

Y is the yellow colour of the skin as measured by the jaundice meter, B the total serum bilirubin concentration, a the reserve albumin concentration, and Y_0 the basic yellowness of the skin at birth.

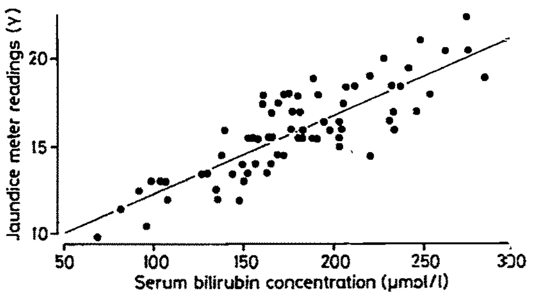


Figure *Correlation between the jaundice meter readings and the serum bilirubin concentration in 76 newborn infants. Regression line: Y=7·75+0·046X.*

can be explained by the presence of bilirubin-albumin in extravascular spaces.

The inverse correlations to the reserve albumin concentration and pH can be understood as a result of bilirubin acid precipitation, as developed in the theoretical section. As the serum bilirubin concentration is not significantly related to reserve albumin or the plasma pH, the effect of a low reserve albumin or a low pH cannot be explained as an indirect one, exerted through an effect of these indices on serum bilirubin concentration. It is likely, therefore, that a direct causal relationship exists between the yellow colour and a low reserve albumin and low pH and that bilirubin in the skin is in part present as precipitated bilirubin acid.

Discussion

Measuring the yellow colour of the skin is not a suitable method for obtaining the plasma bilirubin concentration as the yellow colour depends upon other factors—the reserve albumin concentration, plasma pH, and the basic skin colour—in addition to the plasma bilirubin. According to the figure errors may amount to as much as 93 μmol/l.

Furthermore, the plasma bilirubin concentration is not a suitable predictor of bilirubin encephalopathy.[6 7 20 21] Deposition of bilirubin in the newborn brain depends upon other factors than serum bilirubin concentration—for example, the presence of bilirubin displacing drugs,[22] acidosis,[23 24] etc. It seems necessary, therefore, to discuss the utility of skin colour measurements in the management of icteric infants.

As shown above, it is likely that bilirubin is transferred to the icteric skin of neonates by two mechanisms; leakage of bilirubin-albumin into extravascular spaces and precipitation of bilirubin acid. The first of these mechanisms is probably not active in the brain because the central nervous system has no extravascular albumin space.[25] We cannot, therefore, expect that kernicterus should parallel jaundice of the skin. In the absence of acidosis the skin may become icteric without involvement of the brain, as seen in adults in cases of haemolytic icterus, etc. On the other hand if kernicterus develops in an infant due to high serum bilirubin, low reserve albumin, and acidosis, bilirubin acid will also be deposited in the skin. In consequence, it seems possible that the yellow colour of the skin is correlated with that of the brain, to the extent that bilirubin deposition in the skin has occurred by precipitation of bilirubin acid. If so, the intensity of the yellow colour of the skin may be a somewhat better predictor of brain damage than the serum bilirubin concentration and measurement of the colour of the skin may theoretically be of clinical utility.

We wish to thank Birgitte Bannebjerg Frederiksen for technical work, the nursing and laboratory staff for help in jaundice meter readings and serum bilirubin concentrations measurements, and Frede Nielsen for the drawing. This study was supported by Nordjyllands Amtskommunes Forskningsfond Grant No 2–16–30, and by Niels Jensens Forskningsfond Grant No 5–9–1986.

References

[1] Yamanouchi I, Yamauchi Y, Igarashi I. Transcutaneous bilirubinometry: preliminary studies of noninvasive transcutaneous bilirubin meter in the Okayama National Hospital. *Pediatrics* 1980;**65**:195–202.

[2] Hegyi T, Hiatt IM, Indyk L. Transcutaneous bilirubinometry. Correlations in term infants. *J Pediatr* 1981;**98**:454–7.

[3] Tan KL. Transcutaneous bilirubinometry in fullterm Chinese and Malay infants. *Acta Paediatr Scand* 1982;**71**:593–6.

[4] Hannemann RE. Evaluation of the Minolta bilirubin meter as a screening device in white and black infants. *Pediatrics* 1982;**69**:107–9.

[5] Brown AK, Kim MH, Valencia G, Nuchpuckee P, Boyle G. Factors affecting the transcutaneous measurement of bilirubin: influence of race, gestational age, phototherapy and albumin binding capacity. In: Rubatelli FF, ed. *Neonatal jaundice.* New York: Plenum Publishing Corporation, 1984:95–109.

[6] Lucey JF. Bilirubin and brain damage: a real mess. *Pediatrics* 1982;**69**:381–2.

[7] Kim MH, Yoon JJ, Sher J, Brown AK. Lack of predictive

indices in kernicterus: a comparison of clinical and pathologic factors in infants with and without kernicterus. *Pediatrics* 1980;**66**:852–8.

[8] Katz J, Bonorris G, Sellers AL. Extravascular albumin in human tissues. *Clinical Science and Molecular Medicine* 1970;**39**:725–9.

[9] Smith PC, Frank HA, Kasdon EJ, *et al.* Albumin uptake by skin, skeletal muscle and lung in living and dying patients. *Ann Surg* 1978;**187**:31–7.

[10] Cashore WJ, Oh W, Brodersen R. Reserve albumin and bilirubin toxicity index in infant serum. *Acta Paediatr Scand* 1983;**72**:415–9.

[11] Eriksen EF, Danielsen H, Brodersen R. Bilirubin-liposome interaction: formation of a bilirubin dianion-phospholipid complex, followed by bilirubin acid aggregation. *J Biol Chem* 1981;**256**:4269–74.

[12] Brodersen R. Bilirubin solubility and interaction with albumin and phospholipids. *J Biol Chem* 1979;**254**:2364–9.

[13] Brodersen R. Localization of bilirubin pools in the non-jaundiced rat with a note on bilirubin dynamics in normal human adults and in Gilbert's syndrome. *Scand J Clin Lab Invest* 1972;**30**:95–106.

[14] Brodersen R, Andersen S, Jacobsen C, *et al.* Determination of reserve albumin-equivalent for ligand binding, probing two distinct binding functions of the protein. *Anal Biochem* 1982;**121**:395–408.

[15] Brodersen R, Bartels P. Enzymatic oxidation of bilirubin. *Eur J Biochem* 1969;**10**:468–73.

[16] Anonymous. *Minolta/Air-Shields Jaundice Meter 101 operators manual.* Hatboro, Pennsylvania: Narco Scientific, Air-Shields Division, 1981.

[17] Ebbesen F. The relationship between the cephalo-pedal progress of clinical icterus and the serum bilirubin concentration in newborn infants without blood type sensitization. *Acta Obstet Gynecol Scand* 1975;**54**:329–32.

[18] Doumas BT, Perry BW, Sasse EA, Straumfjord JV. Standardization in bilirubin assays: evaluation of selected methods and stability of bilirubin solutions. *Clin Chem* 1973;**19**:984–93.

[19] Brodersen R, Jacobsen J. Serum bilirubin diglucuronide in the human adult and newborn child. In: Bouchier ID, Billing BH, eds. *Bilirubin metabolism.* Oxford: Blackwell, 1967:111–5.

[20] Brodersen R. Aqueous solubility, albumin binding, and tissue distribution of bilirubin. In: Ostrow JD, ed. *Bile pigments and jaundice. Molecular, metabolic, and medical aspects.* Basel: Marcel Dekker, 1986:157–81.

[21] Ritter DA, Kenny JD, Norton HJ, Rudolph AJ. A prospective study of free bilirubin and other risk factors in the development of kernicterus in premature infants. *Pediatrics* 1982;**69**:260–6.

[22] Brodersen R, Friis-Hansen B, Stern L. Drug induced displacement of bilirubin from albumin in the newborn. *Dev Pharmacol Ther* 1983;**6**:217–29.

[23] Stern L, Denton RL. Kernicterus in small premature infants. *Pediatrics* 1965;**35**:483–5.

[24] Brodersen R, Stern L. Kernicterus research and the basic sciences. A prospect for future development. *Pediatrics* 1987;**79**:154–6.

[25] Maynard EA, Schultz RL, Pease DC. Electron microscopy of the vascular bed of rat cerebral cortex. *Am J Anat* 1957;**100**: 409–34.

Correspondence and requests for reprints to Dr A Knudsen, Kattegatsvej 38, DK-9700 Brønderslev, Denmark.

Accepted 3 October 1988

Archives of Disease in Childhood, 1989, **64**, 610–621

Short reports

Low dose prednisolone in nephrotic syndrome

I A CHOONARA, D HENEY, AND S R MEADOW

Department of Paediatrics and Child Health, St James's University Hospital, Leeds

SUMMARY Sixteen patients with steroid responsive nephrotic syndrome were treated on 29 separate occasions with a low dose of prednisolone (30 mg/m^2/day). All went into remission within 14 days. The duration of remission in the six patients who had had previous relapses treated with a higher dose of prednisolone was similar.

Prednisolone was used for children with nephrotic syndrome in 1956, when Arneil described four children (age 2–8 years) all of whom responded to prednisolone 60 mg daily.[1] Subsequently a dosage of 60 mg/m^2/day has been accepted as standard treatment.[2] There have been several studies that have looked at the effect of duration of prednisolone in relation to long term outcome.[3 4] The dose of prednisolone required to achieve remission has not been studied. The aim of this study was to see whether remission could be induced with half the standard dose of prednisolone.

Patients and methods

New patients with nephrotic syndrome (proteinuria >40 mg/hour/m^2, hypoalbuminaemia <25 g/l, and oedema) who had not previously received corticosteroids from their general practitioner or the referring hospital were entered into the study. Patients with nephrotic syndrome who were attending the Regional Paediatric Nephrology Clinic on a regular basis who had a definite relapse, indicated by a heavy proteinuria (Albustix ++++) for seven consecutive days or oedema in the presence of heavy proteinuria, were entered into the study. Patients were given a single daily dose of prednisolone (30 mg/m^2) each morning. If, after 14 days, there was no remission then the daily dosage was increased to the standard 60 mg/m^2. Remission was defined as three consecutive days without abnormal proteinuria (<4 mg/hour/m^2 (Albustix 0 or trace)). Once remission was induced, the dose of prednisolone was gradually decreased over the next four to six weeks, so that patients were back on maintenance prednisolone (frequent relapsers) or off treatment altogether (new patients).

Eight new patients (age 2–11 years) and nine relapsed nephrotics (age 2–16 years) entered the study. The latter had been diagnosed one to 15 years previously. Seven had received at least one course of cyclophosphamide.

Results

One child had steroid resistant nephrotic syndrome and failed to respond to either 30 mg/m^2/day or 60 mg/m^2/day. The other 16 children all went into remission within 14 days. The median number of days for the induction of remission was seven days (eight for new patients, six for relapsed nephrotics). The 16 patients were treated on 29 separate occasions with low dose prednisolone and consistently went into remission within 14 days. The duration of the remission was shorter for the new patients (1·5–8 months, median 3) than for the relapsed patients (2–17 months, median 6). Three new patients had their first relapse within two weeks of stopping steroids.

The records of those nine patients who had previously been treated with steroids were reviewed in order to determine the duration of remission and the dose of prednisolone used. Two children had been treated previously with 30 mg/m^2/day prednisolone. One patient has been in remission for seven months but as she received cyclophosphamide shortly after going into remission with the low dose of prednisolone her data have not been included. The other six children all received up to 65 mg/m^2/day. The 10 remissions after 30 mg/m^2/day prednisolone (prospective) and 16 remissions (retrospective) after 35–65 mg/m^2/day prednisolone are shown in the figure. Both the mean and the median duration of remission were similar in the low dose (prospective) and standard dose (retrospective) treatments (mean, 6·9 and 7·6 months respectively; median 7·5 and 5·5 months respectively).

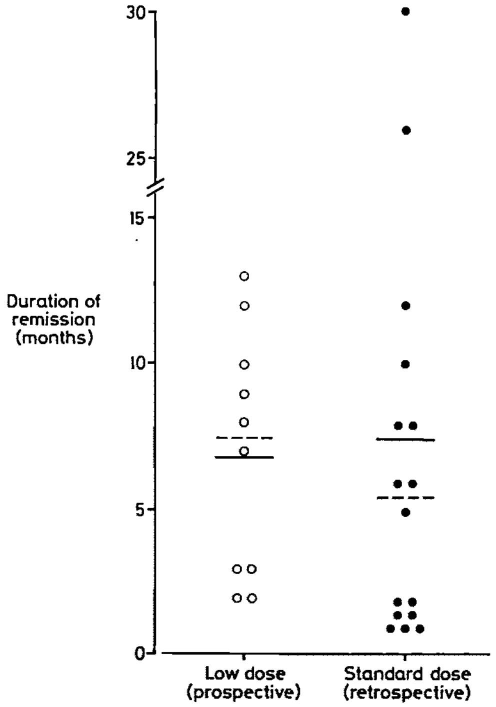


Figure *Duration of remission in six patients after 30 mg/m²/day prednisolone (prospective) (○) and 35–65 mg/m²/day prednisolone (retrospective) (●). The mean (——) and median (– – –) values are shown.*

Discussion

Steroid toxicity is common in children with nephrotic syndrome and is related to both the dose and duration of treatment.[5] Two recent studies have suggested that a longer course of treatment has a favourable effect on the remission period.[3 4] The dose of prednisolone, however, has not been investigated and the standard dose of 60 mg/m²/day has been used in most major studies.[2–4] Prednisolone is often administered in divided doses each day and thus the equivalent single daily dose is greater than 60 mg due to its dose dependent kinetics.[6] These results, albeit in a small number of patients, suggest that in most children with nephrotic syndrome, remission can be induced with a low dose of prednisolone (30 mg/m²/day).

It is not possible to compare directly the prospective data after the low dose prednisolone with the retrospective data obtained from the case notes, as the disease process varies with time. This is clearly shown in the varying duration of remission for the retrospective data. The similarity between the prospective and retrospective data, however, suggests future studies should look at the dose of prednisolone as well as the duration of treatment, both in newly diagnosed nephrotics and also in cases of relapse.

We thank Miss Tracy Watson for typing the manuscript.

References

[1] Arneil GC. Treatment of nephrosis with prednisolone. *Lancet* 1956;i:409–11.

[2] International Study of Kidney Disease in Children. Controlled trial of azathioprine in children with nephrotic syndrome. *Lancet* 1970;i:959–61.

[3] Arbeitsgemeinschaft fur Padiatrische Nephrologie. Short versus standard prednisone therapy for initial treatment of idiopathic nephrotic syndrome in children. *Lancet* 1988;i:380–3.

[4] Ueda N, Chihara M, Kawaguchi S, *et al.* Intermittent versus long term tapering prednisolone for initial therapy in children with idiopathic nephrotic syndrome. *J Pediatr* 1988;**112**:122–6.

[5] Spirer Z, Hauser GJ. Corticosteroid therapy in pediatric practice. *Adv Pediatr* 1985;**32**:549–87.

[6] Frey FJ, Ruegsegger MK, Frey BM. The dose-dependent systemic availability of prednisone: one reason for the reduced biological effect of alternate-day prednisone. *Br J Clin Pharmacol* 1986;**21**:183–9.

Correspondence to Dr I A Choonara, Division of Clinical Pharmacology, University Hospital, S-751 85 Uppsala, Sweden.

Accepted 4 November 1988

612 *Archives of Disease in Childhood,* 1989, **64**

Does dexamethasone suppress the ACTH response in preterm babies?

J M RENNIE,[*] B BAKER,[†] AND A LUCAS[†]

Department of [*]Paediatrics and [†]Dunn Nutritional Laboratory, University of Cambridge and Medical Research Council

SUMMARY Tests of adrenal stimulation with adrenocorticotrophic hormone (ACTH) were performed before and after commencing dexamethasone treatment in 12 infants. All except one of the tests performed showed the expected twofold rise in serum cortisol, suggesting that in this group of premature babies dexamethasone did not suppress the adrenal response.

Dexamethasone treatment has been shown to be effective in reducing the respiratory support required by infants who are still ventilator dependent at 3 weeks postnatal age.[1] The dose recommended as a result of such studies is high, treatment usually commencing with 0·5 mg/kg/day. Preterm babies are often subject to intercurrent stress from surgery or infection and in view of the increasing use of dexamethasone treatment for bronchopulmonary dysplasia it seemed important to document whether such treatment resulted in adrenal suppression. A short ACTH test has been shown to be reliable in predicting the stress response to surgery in adult patients.[2] The preterm infant is normally capable of responding to ACTH at a dose of 36 µg/kg with a two to threefold rise in serum cortisol concentration at one hour,[3] and so this method was chosen to evaluate adrenal response in a group of dexamethasone treated babies.

Subjects and methods

A group of 12 preterm infants who had been treated in the Cambridge neonatal intensive care unit during 1986–7 were studied. They had a mean gestational age of 26 weeks (range 23–29 weeks) and mean birth weight of 968 g (range 616–1735 g). The ventilatory support required before the administration of dexamethasone was positive pressure ventilation in 10 and an inspired oxygen of >30% in two. Mean postnatal age at the start of treatment was 22 days (range from 9–45 days). Courses lasted a mean of 13 days (range 3–28 days) with a dose regime similar to that used by Avery *et al:* commencing with 0·5 mg/kg/day given intravenously in two divided doses for three days, then with a 10% dose reduction 72 hourly until the end of the course.[1] Ventilatory support was reduced after treatment in seven babies. There were four positive blood cultures after commencement of treatment, and one gastrointestinal perforation. Seven of the infants did not survive in the long term, one remaining ventilated in 80% oxygen at the age of 7 months, and one has cerebral palsy at 18 months. Only three of the babies had a normal outcome.

ACTH (Synacthen) was given in a dose of 36 µg/kg intramuscularly and venous or arterial blood samples drawn for cortisol estimation before and one one hour after the dose.[3] Tests were performed at midnight before, during, and after treatment. Two of the babies had samples collected shortly before the end of a course, and 10 had samples collected between five and 28 days after treatment had ceased. Serum cortisol was determined on duplicate 25 µl samples by radioimmunoassay (Gamma-BCT cortisol kit, RIA (UK) Ltd). Cross sensitivity of antibody was: prednisolone 28%, corticosterone 8%, prednisone 2·1%, and dexamethasone <0·05%. For comparison of groups of cortisol values the Mann-Whitney rank sum test was used. The study was approved by the local ethical committee.

Results

Both before and after treatment all except one of the ACTH tests showed the expected twofold rise in cortisol concentration (figure). Median and interquartile range of cortisol before treatment was 98 nmol/l (83–131) rising to 544 nmol/l (77–229) and after treatment 105 nmol/l (76–229) rising to 603 nmol/l (496–717). There was thus no evidence of blunting and there was a significant rise in both groups (p=0·01, Mann-Whitney). No relation was observed between either serum cortisol concentration or the degree of the response with postnatal age or duration of dexamethasone treatment.

Discussion

In this group of premature babies dexamethasone

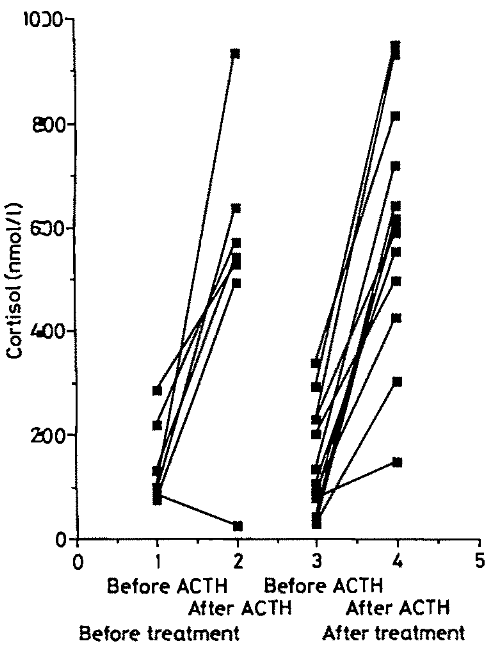


Figure *Serum cortisol concentration before and after ACTH in babies treated with dexamethasone and before and after steroid treatment.*

treatment did not suppress or blunt the cortisol response to ACTH up to 28 days after cessation of treatment. Even in the subgroup of five infants tested between two days before and seven days after the end of treatment no suppression was seen. This was a surprising finding as we used the relatively high dose of dexamethasone recommended for bronchopulmonary dysplasia. Furthermore it was interesting that basal cortisol concentrations were the same before and after treatment, although these data do not preclude a fall in plasma cortisol during treatment.

The daily dose of dexamethasone used here and in similar studies would be equivalent to a prednisolone dose of 3 mg/kg/day.[1] Adult patients treated with 25 mg twice daily (less than 1 mg/kg) exhibited a blunted cortisol response.[4] The cortisol response in infants has been shown to be preserved after maternal betamethasone treatment,[5] although the cord blood cortisol concentration was suppressed. Furthermore, in the study of Thomas *et al* five ill infants still mounted an adequate response to ACTH despite absent basal cortisol concentrations.[3] One possible explanation for these and our own findings might be that the ACTH stimulus was relatively larger than that normally applied in adults. The dose of ACTH required to produce a cortisol response similar to that of hypoglycaemia in adults is only 0·2 μg/kg intravenously, suggesting that the usual dose of 250 μg (5 μg/kg) for an adult ACTH test is far in excess of that needed to raise a response. Probably in all the ACTH regimes commonly used in adults and children the dose of ACTH is larger than the amount required to stimulate the adrenal, so that the lack of dexamethasone suppression observed in this study is unlikely to relate to the dose of ACTH chosen. At the time that the babies in this study were investigated the hyperaemic fetal zone of the adrenal gland would not have involuted to the half size that is documented at one month,[6] and it may be that this was the reason for the preserved response.

The objective of this study was to examine the cortisol response after dexamethasone treatment; while we cannot comment on the response during treatment, these preliminary data suggest that after a complete course of dexamethasone treatment steroid replacement therapy for intercurrent infection or surgery may not always be necessary.

References

[1] Avery GB, Fletcher AB, Kaplan M, *et al.* Controlled trial of dexamethasone in respirator-dependent infants with bronchopulmonary dysplasia. *Pediatrics* 1985;**75**:106–11.

[2] Kehlet H, Binder C. Value of an ACTH test in assessing hypothalamic-pituitary-adrenal function of glucocorticoid-treated infants. *Br Med J* 1973;**ii**:147–9.

[3] Thomas S, Murphy JF, Dyas J, *et al.* Response to ACTH in the newborn. *Arch Dis Child* 1986;**61**:57–60.

[4] Streck WF, Lockwood DH. Pituitary adrenal recovery following short-term suppression with corticosteroids. *JAMA* 1979;**66:** 910–3.

[5] Ballard PI, Gluckman PD, Liggins GC, *et al.* Steroid and growth hormone levels in premature infants after prenatal betamethasone therapy to prevent respiratory distress syndrome. *Pediatr Res* 1980;**14**:122–7.

[6] Winter JSD. The adrenal cortex in the fetus and neonate. In: Anderson DC, Winter JSD, eds. *Adrenal cortex.* London: Butterworths, 1985:32–56.

Correspondence and requests for reprints to Dr J M Rennie, Department of Paediatrics, University of Cambridge, Level 8, Addenbrooke's Hospital, Hill's Road, Cambridge CB2 2QQ.

Accepted 1 December 1988

614 *Archives of Disease in Childhood,* 1989, **64**

Nephrocalcinosis in Shwachman's syndrome

C T D'ANGIO AND J K LLOYD

Hospital for Sick Children, Great Ormond Street, and Institute of Child Health, University of London, London

SUMMARY Nephrocalcinosis has been reported only infrequently in Shwachman's syndrome. We describe a case in which nephrocalcinosis occurred and speculate that this may be due to increased urinary oxalate excretion.

The syndrome of exocrine pancreatic insufficiency and bone marrow dysfunction was first described by Shwachman and colleagues in 1964, and subsequently other features such as bone dysplasia have been recognised.[1] In 1980, Aggett *et al* reviewed a series of 21 patients, one of whom was found to have nephrocalcinosis at necrospy.[2] We report another child with Shwachman's syndrome in whom nephrocalcinosis was an early feature.

Case report

A boy, weighing 3300 g, who was the second son of healthy, unrelated parents was born after a normal pregnancy, labour, and delivery. He was initially fed orally on a standard infant formula, but feeding became increasingly difficult and he failed to thrive. At 6 weeks of age, he was admitted to hospital, where he continued to gain weight poorly despite numerous feed changes.

Nasogastric feeding was therefore started at 10 weeks of age. Investigations showed intermittent neutropenia (the lowest concentration was $<0\cdot2\times10^9$ neutrophils/l), persistently low serum immunoreactive trypsin (0–2 µg/l), and mildly raised plasma alanine transaminase and aspartate transaminase activities. Sweat sodium and chloride concentrations were normal. A radiograph of the chest showed broadened anterior ends of the ribs.

A diagnosis of Shwachman's syndrome was made and he was treated with pancreatic enzyme supplements from 4 months of age. Severe feeding difficulty and failure to thrive persisted, however, and at 7 months he was referred to us for further investigation. On admission his weight (5450 g), length (60 cm), and head circumference (42 cm) were all below the third centile. He had a narrow chest with Harrison's sulci, mild subcostal recession, increased tone in the legs with brisk reflexes and ankle clonus, and mild hirsutism. His liver was not enlarged. Pancreatic enzyme supplements were withheld on admission. Shwachman's syndrome was confirmed by low bicarbonate production (maximum 16 mmol/l), low lipase activity (maximum 13 µmol/min/ml), and absent trypsin activity in duodenal fluid obtained after stimulation with secretin and cholecystokinin, together with intermittent neutropenia and typical radiological changes in the ribs. His transaminases were moderately raised (alanine transaminase 187 IU/l, and aspartate transaminase 122 IU/l). Immunological investigation showed poor neutrophil mobility. Further evaluation of the urinary tract was undertaken (see below) and pancreatic enzyme supplements were restarted at 8 months of age.

RENAL INVESTIGATIONS AND MANAGEMENT

Brightly reflective areas around the renal pyramids consistent with nephrocalcinosis had originally been observed in both kidneys on ultrasound examination at the age of 2½ months. At that time the urine was sterile and a spontaneous urinary pH of 5 was observed. Glycosuria or aminoaciduria were not present. The 24 hour urinary oxalate excretion was 0·31 mmol/1·73 m^2 surface area/24 hours (normal $\leq$0·46 mmol/1·73 m^2 surface area/24 hours). The 24 hour urinary calcium excretion was normal, as were the plasma urea and creatinine concentrations.

Further renal ultrasound examinations at the ages of 3 and 5½ months continued to show nephrocalcinosis, more noticeable on the left than on the right. At 7½ months, ultrasound examination showed nephrocalcinosis on the left side only; computed tomography of the abdomen performed at the same time confirmed the left sided nephrocalcinosis. Both investigations also showed dilatation of the right renal pelvis and ureter. A stone was visible in the right distal ureter on plain radiographs and computed tomograms.

The urine remained sterile, without aminoaciduria or glycosuria. Urinary calcium to creatinine ratio was 0·097 mmol/mmol (normal range 0·060–0·740 mmol/mmol), and oxalate excretion was 0·40 mmol/1·73 m^2 surface area/24 hours. At 8 months a right ureterolithotomy was performed. Analysis of the stone showed it to be 90% calcium oxalate.

At 11 months, after three months of continuous pancreatic supplementation, the urinary oxalate had fallen to 0·23 mmol/1·73 m^2 surface area/24 hours and renal ultrasound showed a decrease in the left sided nephrocalcinosis. Urinary calcium to creatinine ratio was 0·10 mmol/mmol.

Discussion

Renal abnormalities have only rarely been recognised in Shwachman's syndrome. Aggett *et al,* in their review of 21 children with Shwachman's syndrome, described 10 children with intermittent and variable glycosuria.[2] Two children had mild, generalised aminoaciduria and one of these also had tubular acidosis. Marra *et al,* also described a patient with type I renal tubular acidosis.[3] Nephrocalcinosis appears to have been reported only once previously and this was at necropsy; no data are available regarding this child's renal function during life.[2]

Hyperoxaluria and renal oxalate stone formation are common in adults with intestinal disease, particularly that of the ileum.[4] Fat malabsorption is felt to be the basis of the hyperoxaluria seen in intestinal disease. Long chain fatty acids passing into the colon form soaps with calcium, depriving oxalate of its usual cation and thus increasing its absorption.[5] Ogilvie *et al* measured urinary oxalate in 62 children with fat malabsorption. Five of the children had pancreatic dysfunction (two with cystic fibrosis, two with Shwachman's syndrome, and one with congenital isolated lipase deficiency). Both of the children with Shwachman's syndrome had hyperoxaluria; one of these was studied again after treatment with pancreatic enzymes and a low fat diet with added medium chain triglycerides, and his oxalate excretion was found to have returned to normal. In none of the children in that study were renal stones shown.[6]

Our patient showed nephrocalcinosis and produced a stone consisting largely of calcium oxalate. His urinary calcium concentration was normal and he had no evidence of a renal tubular dysfunction or acidosis. Although hyperoxaluria could not be shown, excessive excretion of oxalate would appear the most likely cause of his calculi, and the fall in urinary oxalate on pancreatic enzyme supplementation with comcomitant reduction in the degree of nephrocalcinosis supports this hypothesis. This case provides a link between the hyperoxaluria previously described in Shwachman's syndrome[6] and the report of nephrocalcinosis discovered on necropsy.[2] The possibility of Shwachman's syndrome should be considered in a child with nephrocalcinosis and failure to thrive, and children known to have Shwachman's syndrome should have periodic urinary oxalate estimations and possibly also renal ultrasound examinations.

We thank Drs HC Spratt and CJ Rolles for referring the patient and Professor TM Barratt for helpful suggestions.

References

[1] Shwachman H, Diamond CK, Oski FA, Khaw KT. The syndrome of pancreatic insufficiency and bone marrow dysfunction. *J Pediatr* 1964;**65**:645–63.

[2] Aggett PJ, Cavanagh NPC, Matthew DJ, Pincott JR, Sutcliffe J, Harries JT. Shwachman's syndrome: a review of 21 cases. *Arch Dis Child* 1980;**55**:331–47.

[3] Marra G, Appiani AC, Romeo L, *et al.* Renal tubular acidosis in a case of Shwachman's syndrome. *Acta Paediatr Scand* 1986;**75**: 682–4.

[4] Smith LH, Fromm H, Hofmann AF. Acquired hyperoxaluria, nephrolithiasis, and intestinal disease. *N Engl J Med* 1972;**286**: 1371–5.

[5] Silverman A, Roy CC. Malabsorption syndrome. *Pediatric clinical gastroenterology.* 3rd ed. St Louis: CV Mosby, 1983: 249–303.

[6] Ogilvie D, McCollum JPK, Packer S, *et al.* Urinary outputs of oxalate, calcium, and magnesium in children with intestinal disorders. Potential cause of renal calculi. *Arch Dis Child* 1976;**51**:790–5.

Correspondence to Professor JK Lloyd, Institute of Child Health, 30 Guilford Street, London WC1N 1EH.

Accepted 26 October 1988

Successful treatment after 'drowning' in sand

A AVITAL, C SPRINGER, P MOGLE, AND S GODFREY

Department of Pediatrics, Hadassah University Hospital, Jerusalem, Israel

SUMMARY A 30 month old boy who aspirated a large amount of dirty sand was successfully resuscitated and made a full recovery.

Sand and dirt aspiration as a result of accidental burial may be massive and fatal despite intensive treatment including intubation and bronchoscopy.[1 2] Conservative treatment in sand aspiration has also been proposed.[3] We present a case of a young child who 'drowned' in a sand box at kindergarten and was successfully resuscitated.

Case report

A 30 month old boy, who had been previously healthy, was found lying prone in the sand box of his kindergarten shortly after he had been seen playing there. He was cyanotic and gasping with his mouth completely full of sand. He was immediately rushed to our hospital while receiving mouth to mouth ventilation by a passing nurse. In the emergency room he was found to be comatose, with normal size pupils reacting to light, and he was severely cyanotic with a weak and rapid pulse. He was ventilated first by face mask and then through an endotracheal tube. His mouth, pharynx, and larynx were packed with sand and small stones which had to be removed with forceps so as to make the intubation possible. He was transferred while ventilated to the operating room and an emergency bronchoscopy was performed. The child was initially deeply cyanosed and the chest barely moved despite high pressure ventilation through the bronchoscope. Large amounts of sand were removed with forceps from the trachea and main bronchi. Every lobar bronchus was also plugged. The sand was removed by repeated washings. As each lobar orifice was cleaned the chest moved more and the colour improved. After the bronchoscopy the endotracheal tube was left in place for a day and large amounts of sand were removed by suctioning.

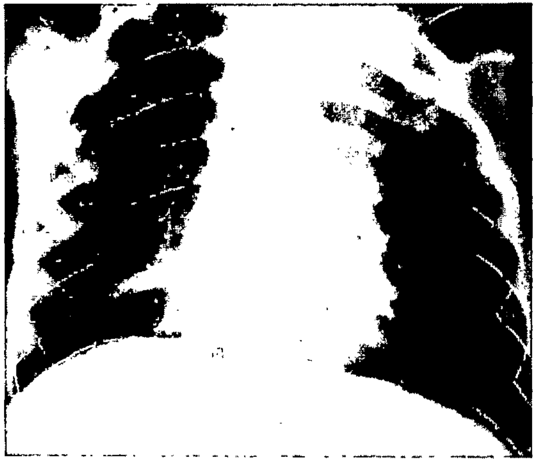


Figure *Chest radiograph of the patient after bronchoscopy.*

The chest radiograph (figure) after the bronchoscopy showed outlining of the left bronchial tree by sand ('bronchogram'). The child was treated with steroids for two days after the bronchoscopy without preventive antibiotic treatment and the recovery was uneventful. The child had intensive chest physiotherapy for one week and was seen later in our respiratory clinic without any complaints and with a normal chest radiograph.

Discussion

In Israel there are 33 fatal cases of asphyxia in children per year. This accounts for 24% of all fatal accidents in children.

Sand boxes in kindergartens are very common. Although they carry the risk of accidental sand aspiration it is very unusual, and to our knowledge this is the only serious case reported in Israel. It was impossible to find any clues to explain why this boy suffered this unusual accident. It may be very important, however, to permit young children to play in sand boxes only under the supervision of their teachers.

In the present case the initial mouth to mouth resuscitation most probably saved his life but also impacted the aspirated sand bolus further inside the lungs. What is remarkable is the total recovery despite the massive aspiration of dirty sand.

References

[1] Bergeson PS, Hirchcliffe WA, Crawford RF, *et al.* Asphyxia secondary to massive dirt aspiration. *J Pediatr* 1978;**92**:506–7.

[2] Van Dyke JJ, Lake KB. Survival after asphyxia secondary to gravel aspiration. *Arch Intern Med* 1976;**136**:471–3.

[3] Bender EM, Kashuk JL. Conservative management of sand aspiration: case report. *Milit Med* 1984;**149**:98–9.

Correspondence to Professor S Godfrey, Department of Pediatrics, Hadassah University Hospital, POB 24035, Jerusalem 91240, Israel.

Accepted 1 November 1988

Ultraviolet irradiation for hepatic rickets

S W KOOH,* E A ROBERTS,* D FRASER,* J CURTIS,* G JONES,† J L WEBER,* AND B J REILLY‡

*Departments of *Paediatrics, †Biochemistry, and ‡Radiology, University of Toronto, and The Hospital for Sick Children, Toronto, Ontario, Canada*

SUMMARY An infant with chronic cytomegalovirus hepatitis and a child with atypical Alagille's syndrome had vitamin D deficiency rickets due to malabsorption. Both received ultraviolet irradiation. This treatment corrected biochemical abnormalities and healed the rickets. In the infant use of a sunlamp at home maintained normal 25 hydroxyvitamin D for over a year. Our study shows that ultraviolet irradiation is an effective treatment of hepatobiliary rickets.

Vitamin D deficiency rickets is a common complication of chronic hepatobiliary disease in children.[1, 2] We and others have shown that the cause of the vitamin D deficiency is malabsorption of vitamin D, not impairment of hepatic hydroxylation.[3] We have shown that intravenous injection of physiological doses of vitamin D can cure rickets in children with hepatobiliary disease. The present study assessed the effectiveness of ultraviolet irradiation in two children with hepatobiliary rickets.

Case reports and methods

CASE 1

An 11 month old girl was admitted to hospital with pathological fractures of long bones. She was known to have had chronic cytomegalovirus hepatitis since birth. A liver biopsy specimen at 3 months of age had shown giant cell transformation of hepatocytes as well as hepatocyte necrosis and focal fibrosis. Later biopsy confirmed the presence of cirrhosis. She was deaf, small, and jaundiced, and had hepatosplenomegaly, a rachitic rosary, and pain in the left arm and leg. She had been receiving 600 U of vitamin D daily by mouth.

Plasma total bilirubin concentration was 203 µmol/l and direct bilirubin was 178 µmol/l. Alkaline phosphatase activity was 2300 U/l, aspartate aminotransferase activity 300 U/l, and bile acid concentration 39 µmol/l. Plasma calcium concentration was 1·64 mmol/l, phosphate 0·81 mmol/l, 25 hydroxyvitamin D 4 nmol/l (reference range 20–80 nmol/l), and parathyroid hormone 110 pmol/l (reference range 3–25 pmol/l). She had generalised aminoaciduria and faecal fat was 40% of intake. Skeletal radiographs showed severe osteoporosis, florid rickets, and fractures of the left humerus and femur. The patient received ultraviolet irradiation daily in hospital for 32 days (for technique see below). She continued it daily at home for a year with a sunlamp.

CASE 2

An 8 year old boy, known to have atypical Alagille's syndrome, was admitted to hospital for investigation of rickets. He had a triangular face with prominent forehead, deep set eyes, mild hypertelorism, and a small chin. He had deep jaundice, anaemia, hepatosplenomegaly, bleeding gums, muscle weakness, ataxia, absent tendon reflexes, and genu valgum. Previous investigations had indicated vitamin K and E deficiencies. A liver biopsy specimen showed a paucity of interlobular bile ducts and cholestasis. Faecal fat was 66% of intake. The patient had been receiving 11 000 U vitamin D daily by mouth.

Concentration of plasma total bilirubin was 520 µmol/l and direct bilirubin 360 µmol/l. Alkaline phosphatase activity was 240–680 U/l and aspartate aminotransferase activity 200 U/l. Plasma calcium concentration was 2·25 mmol/l, phosphate 0·64 mmol/l, and 25 hydroxyvitamin D undetectable. Radiographs showed mild rickets. The patient received ultraviolet irradiation in hospital for 44 days.

ULTRAVIOLET TREATMENT

In hospital ultraviolet treatment was applied with a Burdick lamp UV 800 (Burdick Corporation). The manufacturer stated that this generates an ultraviolet spectrum of 220–320 nm, two thirds of it in the region of 280–320 nm. Lamp to skin distance was 75 cm. The full body, excluding the head and neck, was irradiated. The irradiation started at 20 seconds and rose to 10 minutes each anteriorly and posteriorly.

The sunlamp used at home by case 1 was purchased from Hanscroft (Ajax), and the manufacturer stated that it generates 26% ultraviolet B (290–320 nm) and 70% ultraviolet A (320–400 nm). Lamp to skin distance was 60 cm. The daily ultraviolet dose was 10 minutes each anteriorly and posteriorly during the first months at home, but was reduced to 3 minutes anteriorly as a maintenance dose.

Results

In case 1 the ultraviolet irradiation made the skin erythematous at first and later tanned. The patient began to move the fractured limbs within a few weeks of starting treatment. The biochemical response to ultraviolet irradiation is shown in fig 1. All the measurements started to improve within a few days, and, with the exception of alkaline phosphatase, maximum improvement was achieved in one month despite repeated respiratory infections and continuing hepatic dysfunction. The severe rickets (fig 2a) improved within two weeks (fig 2b) and resolved in six months (fig 2c). One year after starting ultraviolet treatment the patient was maintaining normal concentrations of plasma 25 hydroxyvitamin D (40 mmol/l), calcium (2·42 mmol/l), and phosphate (1·5 mmol/l). The patient continued to have jaundice, hepatosplenomegaly, and abnormal liver function tests.

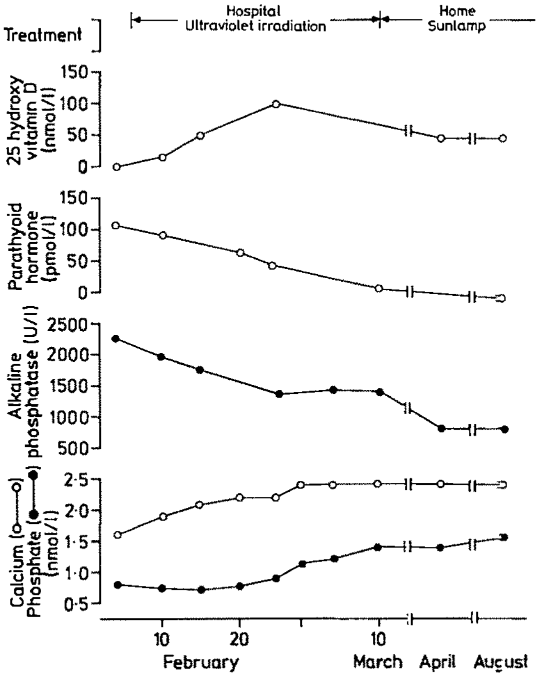


Fig 1 *Biochemical response in case 1. The graph shows correction of the abnormalities in response to ultraviolet irradiation in hospital and maintenance of normal chemistry for six months using sunlamp treatment at home.*

In case 2 the skin became erythematous and dry. During treatment normocalcaemia was maintained and plasma phosphate concentration rose to 1·52 nmol/l. The low plasma 25 hydroxyvitamin D concentration became normal (50 nmol/l) during the ultraviolet irradiation. After discharge from hospital the 25 hydroxyvitamin D concentrations gradually fell. Although no follow up study could be done, it is known that his liver disease worsened and he died from liver failure and uncontrollable haemorrhage two years later.

We measured plasma vitamin D and 25 hydroxyvitamin D concentrations simultaneously before and during ultraviolet irradiation in case 2: before ultraviolet treatment vitamin D was <2·5 nmol/l and 25 hydroxyvitamin D 5·7 nmol/l, and during treatment vitamin D was 22 nmol/l and 25 hydroxyvitamin D 25·5 nmol/l.

Discussion

This study shows that ultraviolet irradiation can cure

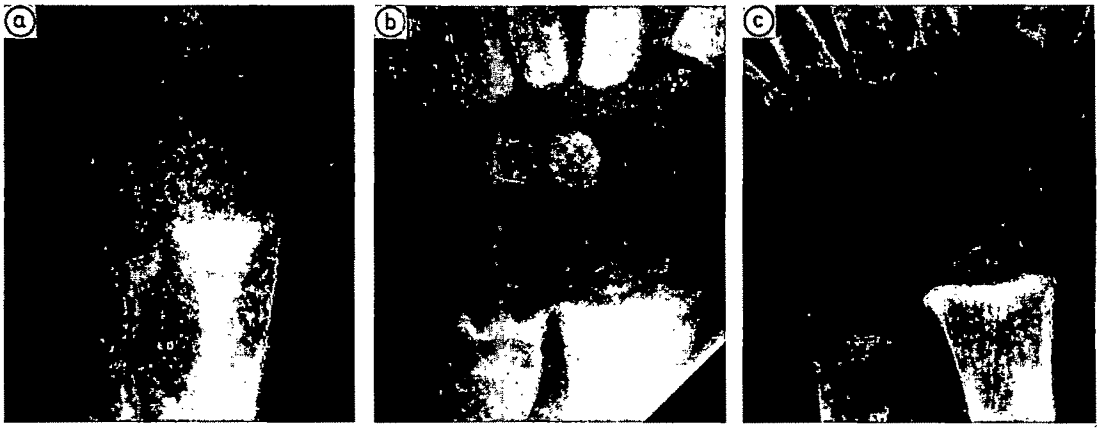


Fig 2 *Sequential radiographs of the wrist in case 1: a, before treatment, showing cupping and fraying of metaphyses; b, two weeks later, during ultraviolet treatment, showing calcification at the metaphysis; and c, two months after starting ultraviolet irradiation. Rachitic lesions have disappeared.*

hepatobiliary rickets. Jaundice did not interfere with cutaneous generation of vitamin D. Both patients had developed vitamin D deficiency rickets even though they had been receiving supraphysiological doses of vitamin D by mouth. Comparison of plasma vitamin D and 25 hydroxyvitamin D concentrations indicated no accumulation of vitamin D. Thus there was no evidence that a defect in hepatic 25-hydroxylation was responsible for the low 25 hydroxyvitamin D concentrations.

Most patients with mild malabsorption of vitamin D can be treated with an increase in oral vitamin D. Some investigators prefer using 25 hydroxyvitamin D because it is more polar and slightly better absorbed. If malabsorption is severe and a child develops vitamin D deficiency while receiving pharmacological doses of vitamin D or 25 hydroxyvitamin D, parenteral vitamin D or ultraviolet treatment are the next alternatives. The choice depends on the availability of the treatment modality. Intravenous vitamin D formulations are investigational, and their administration is inconvenient.

Although ultraviolet irradiation can be achieved from exposure to sunlight, it is generally available only seasonally, and children with chronic liver disease are often too ill to spend much time outdoors. A sunlamp can be an effective substitute and can be purchased at a modest cost. The effective ultraviolet dose to raise 25 hydroxyvitamin D concentrations varies from lamp to lamp[4] and depends on skin pigmentation.[5] The optimal ultraviolet dose can be determined by regular monitoring of 25 hydroxyvitamin D concentrations.

This paper was prepared with the help of the medical publications department, the Hospital for Sick Children, Toronto.

References

1. Kobayashi A, Kawai S, Utsunomiya T, Ohbe Y. Bone disease in infants and children with hepatobiliary disease. *Arch Dis Child* 1974;**49**:641–6.
2. Kooh SW, Roberts EA, Theodossiou M, Reilly BJ, Weber JL. Impact of chronic liver disease on bone mineral metabolism in children. *Journal of Bone and Mineral Research* 1987;**2**:suppl 1, abstract 95.
3. Kooh SW, Jones G, Reilly BJ, Fraser D. Pathogenesis of rickets in chronic hepatobiliary disease in children. *J Pediatr* 1979;**77**:51–8.
4. Devgun MS, Cruickshank AJM, Johnson BE, Paterson CR. Commercially available sun lamps and vitamin D formation. *Postgrad Med J* 1981;**57**:159–63.
5. Clemens TL, Adams JS, Henderson SL, Holick MF. Increased skin pigment reduces the capacity of skin to synthesize vitamin D3. *Lancet* 1982;**i**:74–6.

Correspondence to Dr SW Kooh, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8.

Accepted 3 October 1988

Are babies more satisfied by casein based formulas?

L S TAITZ AND E SCHOLEY

Department of Paediatrics, Children's Hospital, Sheffield

SUMMARY A review of 173 infants who were started on whey based formula showed that 40 (23%) had their feeds changed, usually to a casein based feed by 6 weeks. A double blind randomised trial, comparing casein based with whey based formula confirmed that about 20-25% of babies have their formula changed within six weeks irrespective of the nature of the feed on which the infant was started.

Two types of infant formulas based on cows' milk are now marketed by baby food manufacturers and are officially approved as infant feeds: those which contain mainly casein as their protein and those which are mainly whey based.[1] The latter tend to be more highly modified and resemble breast milk more closely in their chemical composition with lower electrolyte and total protein content and a smaller solute load. It is policy in most maternity units to offer babies whey based formulas but many babies are subsequently switched to casein based formulas.[2]

There appears to be a widespread belief among mothers and some health workers that casein based feeds are in some way more 'satisfying' and so a switch to them in crying, unsettled babies or in infants who have various digestive symptoms such as colic, wind, vomiting, or posseting is not unusual. There may even be a notion that switching to a formula perceived as 'stronger' in some ways indicates progress by the baby. It has recently been suggested that parents may be 'voting with their mouths' in switching from whey to casein based formulas and that perhaps maternity units should 'drop their emphasis on whey dominant milks that are supposedly nearer to breast milk'.[3] The review recommends a blind study to ascertain whether there is a genuine difference in satisfaction between casein and whey based formulas.

This study was undertaken to attempt to determine whether there is any basis to the belief that whey based formulas are more likely to be associated with a 'dissatisfied' baby.

Subjects and methods

This study falls into two parts: a preliminary survey of feeding patterns in normal term infants at their routine, well baby visit at 6 weeks of age, and a prospective, randomised double blind comparison of a whey based formula with two casein based feeds.

PRELIMINARY STUDY

One hundred and seventy three consecutive mothers attending the well baby clinic at the Jessop Hospital, Sheffield were asked if they had changed their baby's feed and the reason for so doing.

PROSPECTIVE STUDY

The study was carried out by a research health visitor (ES). Mothers in the ward who had decided to bottle feed their babies were asked within one day of the birth if they would be willing to participate in the trial. They were informed that the three formulas being tested were all standard feeds already freely available on the market. They were offered a free six week supply of feed and were given three weeks' supply initially to take home. A further three weeks' supply was handed over at a scheduled three week home visit. All the babies were seen again at six weeks and at this point the mother was handed a sealed envelope containing the name of the formula they had been feeding the baby.

Three infant formulas were included in the trial: (A) a casein based formula containing maltidextrin as the source of carbohydrate; (B) a casein based formula with lactose as the carbohydrate source; and (C) a whey based formula. The formulas were packed in plain identical containers labelled A, B, and C. Their contents were unknown to the research health visitor. Allocation of each child was by computer generated random numbers kept by a departmental secretary in no other way involved with the study. All the feeds were approved, commercially produced, and commonly used. Because of packing problems, formula B was introduced into the random allocation later than A and B, accounting for the smaller number of infants in this group.

At enrolment, data were obtained on social background and child bearing history and the baby underwent measurement of weight, head circumference, subscapular and triceps skinfolds. At three weeks and six weeks' visits questionnaires were filled in and the measurements repeated. Statistical analysis was by χ^2, Fisher's exact test, Student's *t* test, and Mann-Whitney U test.

Results

PRELIMINARY STUDY

Of 173 babies 40 (23%) had been changed by 6 weeks of age to a feed other than the (whey based) formula on which they had started. In 30 babies the change was to a casein based formula and in 10 to another whey based feed. In 25 babies changed to a casein based and seven babies changed to another whey based feed there was 'improvement' in the baby. In 29 babies the reason for changing feeds was that the infant was 'not satisfied'.

PROSPECTIVE STUDY

This report is based on the information gathered at birth and at 6 weeks in all 55 babies included in the random allocation. The gestational age and anthropometric data collected at birth and at 6 weeks are

Table *Details of babies studied*

	Formula		
	A	*B*	*C*
	Overall outcome		
Total No	21	14	20
No (%) who changed feed	5 (24)	3 (21)	4 (20)
	Body measurements		
Mean (SE) birth weight (g)	3460 (103)	3430 (120)	3420 (90)
Mean (SE) gestational age (weeks)	39·0 (0·35)	39·5 (0·24)	39·6 (0·27)
Mean (SE) weight at 6 weeks (g)	4780 (120)	4510 (120)	4730 (90)
Mean (SE) head circumference at 6 weeks (cm)	38·4 (0·30)	38·7 (0·32)	38·3 (0·21)
Mean (SE) skinfold thickness at 6 weeks (mm)	7·2 (0·21)	6·6 (0·41)	7·52 (0·29)
	Parental assessment of feeds of babies who did not switch		
No (%) with:	n=16	n=11	n=16
Contented baby	16 (100)	8 (72)	15 (94)
Satisfied baby	15 (94)	7 (64)	14 (88)
Baby who had digestive symptoms	6 (37)	3 (27)	5 (32)

summarised in the table. There were no significant differences between the three groups.

The overall outcome and parental assessment of the infants is also summarised in the table. There was no significant difference between the three milks as regards changes of formula. The apparently increased rate of dissatisfaction with formula B and reduced incidence of gastrointestinal symptoms was not significant.

Discussion

Whey protein accounts for 70% of the protein in human milk, whereas in cows' milk it accounts for only about 20%, the remainder being caseinogen. Some infant formulas (casein based) are made from non-adapted cows' milk while in others (whey based) the milk is adapted to have a protein composition closer to human milk. As whey protein contains a higher proportion of essential amino acids, lower total protein contents are possible. Whey based formulas have a lower solute load than casein based but both types of milk are considered satisfactory infant feeds. One study has, however, found better weight gain in infants fed whey based feeds.[4] The differences were small and the significance of the findings for infants are not clear.

In the present study no significant differences were noted in rates of weight gain in infants fed casein or whey based feeds. In both groups of infants, however, there was a tendency for between one fifth and a quarter of babies to undergo a switch in feeds. The proportion of those switching was similar in the three allocation groups and the preliminary study where the initial formula (whey based) was different from that used in the prospective study. Furthermore, this proportion is similar to that in the survey by the Office of Population Censuses and Surveys on infant feeding for 1985. Data from the United States indicates that a similar proportion of bottle fed babies have their formula changed, usually to a soya based feed.[5] Whereas in Britain lack of satisfaction is the reason usually given for changing, in the United States it is usually ascribed to 'cows' milk allergy'. The difference is probably explained by the fact that the babies in the American study came mainly from middle class families whereas those in the present study were from a lower socioeconomic group. The American mothers were probably more aware of the possibility of 'allergy' as an explanation for their babies' symptoms (usually excessive crying) ascribed to 'lack of satisfaction' by the British mothers. It is interesting that about as many mothers in the American study who changed their babies to soya expressed approval of the change as British mothers whose babies were switched to either casein or whey based milk feeds. These findings indicate that there are a variety of reasons, unrelated to the nature of the feed but wrongly ascribed to the contents of the bottle, which lead to formula switching with a built in tendency for a proportion of mothers to do so. Paediatricians have long advised against speculative changes of formula for many good reasons.[6] The findings of this paper should add to their resolve.

We wish to thank the nursing staff at the Jessop Hospital for their collaboration and Milupa for providing the grant which enabled this study to be carried out.

References

1. Raiha NCR. Nutritional proteins in milk and the protein requirements of normal infants. *Pediatrics* 1985;**75**(suppl): 136–41.
2. Martin J, White A. *Infant feeding 1985*. London: HMSO, 1988. (Office of Population Censuses and Surveys.)
3. Anonymous. Present day practice in infant feeding. *Lancet* 1988;**i**:975–6.
4. Gunn TR, Stunzner D. A comparative trial of casein or whey-predominant formulae in healthy infants. *NZ Med J* 1986;**99**: 843–6.
5. Forsyth BWC, McCarthy PL. Problems of early infancy, formula changes, and mothers beliefs about their families. *J Pediatr* 1985;**106**:1012–7.
6. Taitz LS. Soy feeding in infancy. *Arch Dis Child* 1982;**57**:814–5.

Correspondence to Dr LS Taitz, Department of Paediatrics, Children's Hospital, Sheffield S10 2TH.

Accepted 3 October 1988

Archives of Disease in Childhood, 1989, **64,** 622–628

Personal practice

Management of diabetes mellitus

D I JOHNSTON

Children's Department, University Hospital, Queen's Medical Centre, Nottingham

It is a privilege to introduce insulin treatment to a newly diagnosed diabetic child and to witness the restoration of normal vigour. The daunting task is to impose and sustain a lifelong discipline dedicated not just to the relief of immediate symptoms but to the less tangible goal of improved health some decades later.

We are at a disconcerting phase in our ability to understand and manage insulin dependent diabetes mellitus (IDDM). The disease is occurring with increasing frequency in our young and yet we still know little of its environmental causes. Evidence relating quality of control to late complications continues to accumulate, but we lack the treatment strategies that allow most diabetic children to achieve desired targets of control. The laboratory can provide us with the measures of diabetic control but who are to be judged? Are patients and their families at fault for not being prepared to adjust their lifestyles sufficiently, or are we at fault for setting them unrealistic goals without providing adequate skills and equipment? There are no easy solutions to these dilemmas. There is, however, an obligation to monitor our service as carefully as we monitor an individual's diabetes. We have to steer a careful path, selecting those developments that are appropriate to our young patients but reserving judgment on those that emerge in a wave of enthusiasm but have not been adequately subjected to informed scrutiny.

This paper attempts to select issues of importance in two main areas: aetiology and management. It describes practice within our diabetic clinic, not to emphasise areas in which we feel secure, but to stimulate debate as to the way in which we should evolve.

Aetiology and prevention

It is now established that IDDM results from fluctuating autoimmune injury to the beta cells over months and years before clinical symptoms emerge.[1] Genetic susceptibility is an essential precondition but as yet ill defined environmental factors play the major part in determining which individuals develop IDDM. It has been estimated that while heredity contributes 5–40% of the risk, the environment contributes 60–95%.[2]

Genetic susceptibility is largely, but not entirely, associated with HLA-DR3 and or DR4 on chromosome six. Ninety five percent of white people with IDDM carry DR3 or DR4. These types occur in about 50% of the general population, however, and are therefore of too limited specificity to permit population screening. Closer linkage occurs with the DQ subregion, and it has still to be established whether other genetic markers, for example on chromosome 11, will facilitate prediction. Tarn *et al* have used HLA-DR3, DR4 typing to calculate risk rates in families of index cases.[3] HLA identical relatives have a 16% risk of developing IDDM by age 25 years; haploidentical relatives have a 9% risk, and those not sharing HLA types have almost zero risk. This is a valuable research exercise but has to be seen in the context of only 12–15% of newly diagnosed diabetics having an affected first degree relative.

Although cellular immunity is predominant in causing insulitis and disruption of insulin production, plasma concentrations of islet cell antibodies and complement fixing islet cell antibodies provide markers of the damage. Islet cell antibodies are present in about 80% of newly diagnosed diabetics. Prospective studies within families of index cases have established that islet cell antibody concentrations fluctuate for months and years before diagnosis. The appearance of low titres does not necessarily predict clinical diabetes; however, the detection of high titres of islet cell antibodies or complement fixing islet cell antibodies does suggest more advanced insulitis. Tarn *et al* have estimated the potential yield of screening for islet cell antibodies as being one in 270 per year for first degree relatives, and one in 4000 per year for the general population.[3] The justification for such screening may emerge if properly designed studies establish that we can alter the early natural history of IDDM to provide worthwhile longterm benefit. The measurement of islet cell antibodies does not have a role in forecasting the natural history of established IDDM.

Insulin autoantibodies occur in 18–20% of new diabetics before insulin treatment. They appear to denote susceptibility to autoimmune injury rather than parallel the severity of insulitis.

The nature of the environmental factors remains elusive despite their crucial role and the enormous research effort focused upon them. The increasing incidence of IDDM within the same genetic pool and the social class gradient are two of the findings suggesting the importance of infectious or dietary exposure. The long evolution of IDDM has stimulated interest in slow virus infection. Recent studies point towards cytomegalovirus,[4] and reovirus[5] as being capable of infecting beta cells and provoking hyperexpression of class 1 major histocompatibility proteins.

The role of diet, and in particular cows' milk, remains largely speculative but it is intriguing that minimal cows' milk exposure precipitates beta cell immune damage and diabetes in the BB rat.[5] Behavioural stress is also a trigger factor in the BB rat.

Management at diagnosis

Prompt recognition of diabetic symptoms by families and primary care staff, together with immediate referral to appropriate facilities, has made ketoacidosis at presentation relatively uncommon. The diabetes team can now anticipate the advantage of a relatively well child and a family not overwhelmed by life threatening illness. It is essential that this first encounter between family and diabetes team be carefully planned. Initial explanations and the teaching of practical procedures have a critical role in determining the future motivation and involvement of children and their parents. Ward, clinic, and community based members of the diabetes team must coordinate teaching to ensure that injections are demonstrated in an agreed and uniform manner. Our team has produced a small handbook that encompasses this plan as well as catering for the guidance needed by a new family. There are a number of excellent commercially sponsored handbooks that can be adopted for this purpose.

Our usual practice is to offer a brief admission so that the child and family can benefit from intensive involvement with the team. The emphasis is on the child or parents, or both, performing the injections and capillary blood tests from the outset. The family are also introduced to the principles of good nutrition and a balanced carbohydrate intake. Our diabetes liaison health visitor supervises the transition to home and school. She updates an education checklist and arranges revision in the major areas. We do not provoke hypoglycaemia before discharge, but do emphasise measures to prevent and treat such episodes.

We introduce new diabetics to twice daily insulin injection based on a medium duration human insulin, calculating the initial dosage around 0·5 units/kg/day and dividing it 60% before breakfast and 40% before the evening meal. This alone is sufficient for those presenting with mild metabolic inbalance. In those with greater weight loss and appreciable ketonuria we add short duration insulin equivalent to 0·25 to 0·5 units/kg/day. Children, particularly those with big appetites while restoring body weight, may require initially higher total insulin dosage: 1·0 to 1·5 units/kg/day. With the return of normal activity and appetite we plan downward titration of the dosage guided by symptoms of hypoglycaemia, capillary blood glucose profiles, and concentrations of glycated haemoglobin (HbA_1). The early phase of diabetes management is currently attracting great attention and we are conscious of the emerging evidence that may dictate radical change in our strategy. The evolution of IDDM is such that residual beta cells may retain the ability to produce endogenous insulin for weeks, months, or years after diagnosis. This residual function is responsible for the complete or partial remission phase of early IDDM. Complete remission enables the patient to cease insulin treatment while achieving good control: fasting blood glucose concentration under 7·8 mmol/l, a postprandial concentration under 11 mmol/l, and HbA_1 within the normal range. Complete remission is rare in our experience, and the literature suggests a figure of only 2–3% for paediatric clinics compared with up to 18% in adult series. Recognition depends on how actively clinics pursue insulin reduction.

There is no agreed definition of partial remission, although good control on an insulin dose of no more than 0·25 units/kg/day seems appropriate. Partial remission is common in young diabetics (30–60%) but the duration of remission is very variable: weeks to several years. The younger the child at diagnosis the less likely is sustained remission, probably reflecting more aggressive autoimmune injury or the continuation of provoking environmental influences. Young children are more likely to have HLA-DR4, severe metablic disturbance at presentation, and evidence of a provoking viral infection.[7]

The residual beta cell mass can be estimated using radioimmunoassay measurement of C peptide concentrations in either plasma or urine. Prospective studies show a trend towards early recovery of beta cells after correction of the initial metabolic disturbance, followed by a progressive decline over months or years. Several studies in adult diabetics have linked persistence of detectable C peptide production to better metabolic control and the slower evolution of microvascular complications.[8 9] This relation has been less easy to show in children,[10] and it appears that beta cell function decays more rapidly in children and adolescents.

There is obviously a strong case for exploring treatments that might protect and even allow the regeneration of beta cells. With current insulin regimens the reduced beta cell mass is exposed to the chronic stimulus of hyperglycaemia. This glucotoxicity and the rate at which it is corrected may be key factors in future management. More vigorous treatment at onset is reported to produce a higher rate of remission.[11] What degree of intensive insulin treatment is justified in a newly diagnosed child? There are advocates of prolonged insulin infusion and frequent monitoring after diagnosis.[12 13] Children randomised to continuous subcutaneous insulin infusion treatment from diagnosis, however, showed only modest prolongation of partial remission as compared with those receiving conventional treatment.[14] Those of us who aim for less dramatic early intervention and for prompt home management remain to be convinced.

A range of drugs capable of modifying the immune system are being explored in IDDM. At present the most attractive is cyclosporin. It acts mainly on T cell mediated immunity, and delays the onset of diabetes in BB rats and NOD mice. Two major controlled studies of cyclosporin treatment are underway. An initial report showed that in adults it prolonged the complete remission phase in a fifth of patients.[15] Another French study is examining the value of cyclosporin in children.[16] In a preliminary study using historical controls, 27 out of 40 patients were able to discontinue insulin treatment. Half still did not need insulin at 12 months. It is interesting that the response of young diabetics should appear to be more dramatic than that seen in the parallel adult study. Children were more likely to enter remission if they had shorter duration of symptoms, less weight loss, and milder metabolic disturbance. Response to cyclosporin showed no relation to either HLA types or immune markers.

While these reports are exciting, they should not be regarded as a licence for the widespread use of cyclosporin in diabetic children. There are still important issues to be resolved, and only carefully structured protocols will provide much needed answers. The essential question is whether cyclosporin treatment produces sufficient improvement in the longterm course of IDDM to justify potential drug toxicity? It would be anomalous to expose young diabetics to the risk of cyclosporin induced nephrotoxicity while attemptiing to prevent the onset of diabetic nephropathy in 30–40% of them. Hopefully the unravelling of the immune mechanisms responsible for IDDM, combined with biotechnology, will enable the development of more specific and safer drugs.

The management of established diabetes

In the prepubertal child we continue to favour treatment based on a twice daily injection of mixed short and medium duration insulins. We pay attention to the total dose and avoid exceeding 0·8 units/kg/day; an apparent requirement for greater dosage often points to errors in the balance of insulins used or to other problems of management. The varied lifestyle of young children demands individual and flexible titration of insulin regimens. Some children under 8 years benefit from a bedtime injection of medium duration insulin instead of the pre-evening meal injection.[17] We disagree with the claims that effective control, after the partial remission phase, can be achieved using a single daily insulin injection. Twice daily insulin permits more active insulin adjustment and response to blood glucose monitoring. Our experience is that informed parents of both infants and children elect to use twice daily injection. The more frequent injection regimen enables them to react better to the often unpredictable events and dietary intake of the average child. Information available from long term studies is limited but tends to support the belief that two injections provide better control as judged by the avoidance of late complications.[18] There is also some logic in the argument that the more frequent the injections, the better the preparation for multiple injection regimens that are now being promoted in later life.

The physiological and behavioural adjustments of adolescence combine with diabetes to pose one of the greatest challenges that we face. It is well recognised that insulin requirements tend to rise, often to around 1·5 units/kg/day.[19] Increased growth hormone secretion rather than sex steroids accounts for this phase of increased insulin resistance.[20] Our clinical impression is that girls are more difficult to control, but this may reflect gender differences in exercise and eating behaviour rather than pubertal events. Girls are certainly more susceptible to obesity, and some recognise that the energy loss of poorly controlled diabetes and glycosuria helps them stay slim. These problems have to be anticipated and avoided by sympathetic, realistic dietary guidance. Left unchecked obesity will fuel loss of confidence, disinterest in diabetic control, and more substantial eating disorders.

We are promoting more intensive insulin regimens in teenagers but appreciate that success is dependent on whether we can modify our clinic style to generate interest among these, the most severe of our critics. Our established child and family orientated clinic lacks the necessary flexibility and scope for group participation. We are now offering adolescents the alternative of an early evening open clinic within our local diabetes centre. For those of us who find relating to teenagers in our own family a struggle, the prospect of motivating groups is awesome! Hopefully the task will be shared with young leaders who have emerged from our clinics and attended the Youth Diabetes Project based at Firbush-Loch Tay. The adolescent clinic will also provide a better interface with our colleagues providing a similar service for young adults.

Monitoring control

Most children adjust to the demands of capillary blood glucose monitoring. We recommend a minimum of three to four tests per day twice a week, or one per day the time being varied in an attempt to construct a profile over the week. Naturally enthusiasm wanes with duration of diabetes. Families who are able to make management decisions as the result of these tests are better motivated to persevere. It is important therefore to see the tests as a tool for the instruction of the family rather than as a criterion used by doctors and nurses to make judgments about control. Families can be guided through problem solving exercises—for example, the recognition of potential nocturnal hypoglycaemia or the adjustment of the evening insulin dosage to reduce fasting hyperglycaemia. A few children develop a phobia to capillary punctures. If the answer does not lie with switching to an alternative finger pricking gadget, we have to accept a phase of urine glucose testing. Others falsify tests in an attempt to disguise overeating, or in the belief that the diabetes team will then leave them in peace. Discrepant HbA_1 results and some spot checks at home usually expose falsification. We are beginning to introduce glucose meters equipped with memories for such youngsters but recognise that they will continue in their attempts to outwit us. The real solution lies with our strategies for promoting education and motivation.

Determination of HbA_1 remains the gold standard of diabetes control. Capillary blood is suitable for the assay, and allows regular measurement in clinic or at home visits. Our results are not available in the same clinic but are reviewed a few days later at a follow up meeting of the diabetes team. High and rising values allow us to target our diabetes liaison health visitor's time to greatest effect. The size of our task is shown by the clinic mean HbA_1 concentration that fluctuates between 11·0 and 11·5% (normal range up to 8·0%). We find that the mean rises with age and duration of diabetes. Audit of these clinic values has to take account of the number of adolescents within the children's service.

Serum fructosamine is being promoted as a further index of integrated glycaemia. The assay has the attractions of speed, reproducibility, and reduced cost. The measurement reflects total serum protein, mainly albumin, glycation. It has a shorter half life and is more sensitive to brief hyperglycaemic excursions.[21] These are potential disadvantages in the interpretation of control in childhood, and we do not plan to convert to fructosamine measurement until these doubts have been resolved.

More intensive insulin regimens

Although the relation between long term diabetes control and the development of complications remains a topic of active debate, most of us are sufficiently convinced by the accumulating evidence to wish to promote optimal control. The issue facing paediatricians is whether currently available techniques of diabetes management can be applied to children with sufficient intensity to bring about near normal control within the constraints of an acceptable lifestyle, and without the disruption of repeated severe hypoglycaemia. How near does near normal control have to be to produce real benefit? It is unlikely that there is any simple answer to this question; a different combination of genetic and environmental factors probably determines the threshold of susceptibility to tissue damage in any one individual. Only long term early intervention prospective studies, such as that mounted by the Diabetes Control and Complications Trial Research Group,[22] will resolve this crucial issue. The logistical problems of mounting this study in adult diabetics have been such that it is difficult to entertain such a protocol for young diabetics. Given that microvascular disease is 'programmed' by metabolic conditions early in diabetes, is the prepubertal child relatively protected? There is some evidence to support this. Microalbuminuria, an index of renal glomerular damage, is less prevalent in diabetics under age 12 years compared with those aged over 12 years matched for duration.[23] What this means in the context of setting targets for control before, during and after puberty is unknown. The reality is that we aim for the best control that the child, family circumstances, and available treatment strategies permit.

Continuous subcutaneous insulin infusion has theoretical attractions and it is confirmed that it can produce near normal glycaemic control, at least within the structure of supervised research protocols. It is less certain whether it can be applied with the same good results to the generality of patients in the average clinic setting, and there are certainly major obstacles in its application to children and adolescents.[24] We have had only limited experience in the application of continuous subcutaneous insulin infusion but see our clinic resources as better directed to the promotion of multiple injection regimens based on pen injection devices (NovoPen and NovoPen II). In usual diabetic clinic conditions the control achieved with multiple injection treatment is similar to that while using continuous subcutaneous insulin infusion, but neither is normal.[25 26]

We are actively promoting NovoPen based regimens among older children and adolescents. Short duration insulin is administered before main meals according to simple guidelines. Fifty to sixty percent of the total insulin dose is given as either medium or long duration insulin injected at bedtime. We have used either Monotard or Ultratard, others favour an isophane insulin. The combination of potentially improved control and a more flexible strategy has appeal, but the results are not uniformly successful. Some patients maximise the benefits and sustain improved HbA_1 concentrations. Others exploit the flexibility by embarking on further dietary noncompliance, and add increasing obesity to their problems. Success, as with any regimen, is dependent on motivation and informed use of regular home blood glucose monitoring.

Some of the problems

Hypoglycaemic attacks are an inevitable component of adequately controlled diabetes. There is little data on their incidence in children. Surveys within adult clinics show that 10–15% of patients experience at least one severe episode each year. Attempts at gaining optimal control are accompanied by a two to threefold increase in the frequency of episodes.[22] Although families must be educated to recognise and prevent 'at risk' situations, it is sometimes the case that severe nocturnal attacks occur without warning. Parents should be equipped with the means of raising the blood sugar, glucose gel for buccal mucosa absorption (Hypostop), and glucagon injection. The greater problem is rationalising the threat of recurrence so that parents still retain the target of good control. They can be reassured that acute accidental hypoglycaemia does not cause brain damage even if it manifests as an epileptiform attack. Late evening blood tests particularly after a day of increased physical activity give fairly reliable warning of nocturnal hypoglycaemia. Attention to the total insulin dosage should avoid chronic hypoglycaemia which can be debilitating. Severe hypoglycaemia despite appropriate precautions raises the possibility of intentional overdosage.

Fasting hyperglycaemia and an exaggerated glycaemic response to breakfast is a well recognised problem,[27] and one which generates considerable confusion for families achieving otherwise satisfactory control. Faced with low or normal blood tests at bedtime and at midnight there seems no easy solution. This rise in blood glucose concentration has several causes; a transient decrease in hepatic insulin sensitivity occurring in the early morning hours, a waning of the insulin available from depot preparations, and exaggerated counter regulation provoked by nocturnal hypoglycaemia. The term 'dawn phenomenon' has been coined to describe the early morning rise in blood glucose. Nocturnal surges of growth hormone, which are higher in patients with IDDM, correlate with the changes in hepatic glucose production. Studies with continuous subcutaneous insulin infusion have confirmed the need for a low rate of insulin infusion between 2300 and 0300 hours followed by a phase requiring about 30% increased dosage. Hormonal and neural mechanisms triggered by nocturnal hypoglycaemia (Somogyi phenomenon) add to this process but probably do not play as large a part as was previously thought.

Measures that we use to combat morning hyperglycaemia include delaying the evening mixed injection and meal within the limits tolerated by child and family, and splitting the evening injection so that the medium duration insulin is given as a third injection at bedtime. Neither is consistently effective. Multiple injection regimens incorporating ultralente insulin have a theoretical attraction but do not always succeed. The answer may lie in the development of new delayed release or proinsulin like formulations. For the present we have to accept the problem, avoiding the temptation to make inappropriate upward adjustments in the evening insulin dosage.

Brittle diabetes

At any one time our clinic population of over 200 children and adolescents contains one or two children who require frequent admission because of ketoacidosis. The disruptive nature of their diabetes effects mood, confidence, growth, and education. Their families become trapped within a spiral of uncertainty and anxiety. The diabetes team finds itself devoting increasing efforts in an attempt to help the child and family but sometimes without apparent reward. The problems posed by brittle diabetics have been vividly reviewed.[28] The causes fall into three main categories: diabetes management, coincidental illness, and child-family dynamics. In our experience the first two show themselves relatively easily. Our diabetes health visitor is the key person in exposing and correcting mismanagement in the home. Many adolescents fail to keep to recommended guidelines, and have raised blood glucose and HbA_1 concentrations to reflect this. Almost all claim to be in excellent health, however, and do not admit to disruption of lifestyle. Among the long list of coincidental disorders that may interfere with diabetic stability, we have encountered chronic pyelonephritis, coeliac disease, inflammatory bowel disease, chronic active hepatitis, autoimmune hypothyroidism, and Addison's disease. Careful clinical review together with selected investigations usually shows the problem without there being confusion with personality based brittle diabetes.

We are constantly impressed how well most families faced with conspicuous financial and social adversity cope with diabetes. Brittle diabetics appear to emerge within families that appear at a superficial level to be contented and united. A typical example is an adolescent girl who has required 10 hospital admissions in the last two years. Each episode is precipitated by ketoacidosis that evolves rapidly, and which is readily controlled after admission. Despite acceptable blood glucose control in the ward outpatient control is erratic and punctuated by symptomatic ketosis and resulting days off school. The girl and her mother perform frequent monitoring in their attempts to avert ketoacidosis. No fault can be found in injection technique, and there is no evidence of dosage omission or manipulation. It emerges that child and mother are closely bonded almost to the exclusion of father and other siblings. This enmeshed relationship focuses upon and amplifies the potential threats created by diabetes. Glycaemic excursions become an obsession, and body language is so highly tuned that formal blood testing is hardly required to fuel their anxiety. The mother may already have been conditioned to health awareness by her own or another relative's chronic illness. The father appears as a peripheral figure, working hard to support his family but avoiding the tensions generated by his daughter. Such a scenario reinforces the importance of the diabetes service having ready access to the skills of family therapy. Diagnosis is complex. Treatment is difficult and time consuming. Success is by no means guaranteed even with adequate resources. Fortunately most such girls have a relatively good medium term prognosis for overcoming this chaotic period. Maturity and increasing autonomy make them more resilient.

It is our impression that boys are less likely to have such an enmeshed relationship, and that devious manipulation is the greater factor. For a small number of these difficult diabetics, the solution lies with carefully selected semiresidential schooling.

Complications of diabetes

The natural history of insulin dependent diabetes is such that paediatricians are largely divorced from the problems created by retinopathy, nephropathy, neuropathy, and large vessel disease. Less sophisticated colleagues have a curious misconception that this gap denies us an essential insight into diabetes and its management. The reality is that children's diabetes services are actively mobilising themselves to pursue increasingly good control during the phase of life when it is most difficult to achieve. Most families are only too well aware of the potential threats facing their child. They are regularly exposed to advertisements and media revelations highlighting the likelihood of blindness, amputation, and heart attacks. It requires considerable delicacy to explore these issues with youngsters and their parents.

Our current strategy for detecting complications is relatively conventional but it has the advantage of a computer based patient record system that ensures regular procedures. These include annual eye examination (with dilatation if duration of diabetes is 10 years or more), annual blood pressure measurement, urine screening for infection and proteinuria, skin state, liver size, and assessment of finger joint flexion deformity. We do not plan to screen for microalbuminuria until there is clearer guidance on optimal procedures for sample collection and measurement.

Transfer to the adult diabetes service

We usually arrange to transfer patients between 16 and 18 years of age but remain sensitive to the wishes of those who prefer earlier promotion. Those whose experience of life is rapidly outpacing their carers in the children's service clearly need prompt handover! A common approach to diabetes management and shared support staff facilitate transfer. The computer based record system ensures continuity of documentation and permits us to follow the progress of our ex-patients. The establishment of a local diabetes centre and adolescent clinics will give us an opportunity to explore whether structured handover clinics offer any additional advantage. The unacceptable drop out rate after transfer reminds us that paediatricians and diabetologists must work closely together to ensure that clinics become more attractive to young adults so that the investment of care during childhood is not squandered.

I am grateful to my colleagues in the children's diabetic clinics at University Hospital, Nottingham and Kings Mill Hospital, Sutton-in-Ashfield for their consistent and enthusiastic support. I am especially indebted to Mrs J Noronha and Mrs J Wynford-Jones whose dedicated liaison work has contributed so much to our service.

References

[1] Tarn AC, Smith CP, Spencer KM, Bottazzo GF, Gale EAM. Type 1 (insulin dependent) diabetes: a disease of slow clinical onset? *Br Med J* 1987;**294**:342–5.

[2] Diabetes Epidemiology Research International. Preventing insulin-dependent diabetes mellitus: the environmental challenge. *Br Med J* 1987;**295**:479–81.

[3] Tarn AC, Thomas JM, Dean BM, *et al.* Predicting insulin-dependent diabetes. *Lancet* 1988;**i**:845–50.

[4] Pak CY, Eun HM, McArthur RG, Yoon JW. Association of cytomegalovirus infection with autoimmune type 1 diabetes. *Lancet* 1988;**ii**:1–4.

[5] Campbell IL, Harrison LC, Ashcroft RG, Jack I. Reovirus infection enhances expression of class 1 MHC proteins on human pancreatic beta and rat insulinoma (RIN-m5F) cells. *Diabetes* 1988;**37**:362–5.

[6] Daneman D, Fishman L, Clarson C, Martin JM. Dietary triggers of insulin dependent diabetes in the BB rat. *Diabetes Res* 1987;**5**:93–7.

[7] Eberhardt MS, Wagener DK, Orchard TJ, *et al.* HLA heterogeneity of insulin-dependent diabetes mellitus at diagnosis: the Pittsburgh IDDM study. *Diabetes* 1985;**34**:1247–52.

[8] Knip M, Sakkinen A, Huttenen N-P, *et al.* Post initial remission in diabetic children. *Acta Paediatr Scand* 1982;**71**:901–8.

[9] Sjoberg S, Carlson A, Rosenqvist U, Ostman J. Health attitudes, self-monitoring of blood glucose, metabolic control and residual insulin secretion in type 1 diabetic patients. *Diabetic Medicine* 1988;**5**:449–53.

[10] Sochett EB, Daneman D, Clarson C, Ehrlich RM. Factors affecting and patterns of residual insulin secretion during the first year of Type 1 (insulin-dependent diabetes mellitus in children. *Diabetologia* 1987;**30**:453–9.

[11] Ludvigsson J, Heding LG, Larsson Y, Leander E. C-peptide in juvenile diabetics beyond the postinitial remission period. *Acta Paediatr Scand* 1977;**66**:177–84.

[12] Mirouze J, Renard E, Rodier M. Long-term remission in acute diabetes mellitus of recent onset. *Presse Med* 1987;**16**:1570–3.

[13] Edelmann E, Walter H, Biermann E, Schleicher E, Bachmann W, Mehnert H. Sustained normoglycaemia and remission phase in newly diagnosed type 1 diabetic subjects. Comparison between continuous subcutaneous insulin infusion and conventional therapy during a one year follow-up. *Horm Metab Res* 1987;**19**:419–21.

[14] de Beaufort CE, Bruining GJ. Continuous subcutaneous insulin infusion in children. *Diabetic Medicine* 1987;**4**:103–8.

[15] Feutren G, Papoz L, Assan R, *et al.* Cyclosporin increases the rate and length of remissions in insulin-dependent diabetes of recent onset. *Lancet* 1986;**ii**:119–24.

[16] Bougneres PF, Carel JC, Castano L, *et al.* Factors associated with early remission of type 1 diabetes in children treated with cyclosporin. *N Engl J Med* 1988;**318**:663–70.

[17] Hinde FRJ, Johnston DI. Bedtime insulin injections: an alternative regimen. *Arch Dis Child* 1985;**60**:311–5.

[18] McNally PG, Burden AC, Hearnshaw JR. What causes diabetic renal failure (letter). *Lancet* 1988;**i**:501–2.

[19] Mann NP, Johnston DI. Improvement in metabolic control in diabetic adolescents by the use of increased insulin dose. *Diabetes Care* 1984;**7**:460–4.

[20] Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV. Impaired insulin action in puberty; a contributing factor to poor glycemic control in adolescents with diabetes. *N Engl J Med* 1986;**315**:215–9.

[21] Ashby JP, Firer BM. Is fructosamine a clinically useful test? *Diabetic Medicine* 1988;**5**:118–21.

[22] The DCCT Research Group. Diabetes Control and Complications Trial (DCCT): results of a feasibility study. *Diabetes Care* 1987;**10**:1–19.

[23] Dahlquist G, Refberg S. The prevalence of microalbuminuria in diabetic children and adolescents and its relation to puberty. *Acta Paediatr Scand* 1987;**76**:795–800.

[24] Knight G, Boulton AJM, Ward JD. Experience of continuous subcutaneous insulin infusion in the outpatient management of diabetic teenagers. *Diabetic Medicine* 1986;**3**:82–4.

[25] Bak JF, Neilsen OH, Pedersen O, Bek-Nielsen H. Multiple insulin injections using a pen injector versus insulin pump treatment in young diabetic patients. *Diabetes Res* 1987;**6**:155–8.

[26] Marshall SM, Home PD, Taylor R, Alberti KGMM. Continuous subcutaneous insulin infusion versus injection therapy: a randomised cross-over trial under usual clinic conditions. *Diabetic Medicine* 1988;**4**:521–5.

[27] Francis AJ, Home PD, Walford S, Alberti KGMM, Mann N, Reeves WG. Prevalence of morning hyperglycaemia: determinants of fasting blood glucose concentrations in insulin-treated diabetics. *Diabetic Medicine* 1985;**2**:89–94.

[28] Tattersall R. Brittle diabetes. *Br Med J* 1985;**291**:555–7.

Correspondence to Dr D I Johnston, Children's Department, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH.

Archives of Disease in Childhood, 1989, **64,** 629

Neonatology—then and now *(C H M Walker)*

Assisted ventilation in the newborn (1964)

Assisted ventilation in terminal hyaline membrane disease

MARIA DELIVORIA-PAPADOPOULOS AND PAUL R SWYER

Hospital for Sick Children and University of Toronto, Toronto (Arch Dis Child 1964;**39:**481–4)

Goldsmith and Karotkin[1] researched the history of assisted ventilation and found that a record of mouth to mouth methods goes back to Old Testament times, and Hippocrates himself reported his experience with tracheal intubation to support pulmonary function. These skills were ignored for about 2000 years as it was not until the 16th century that attention was again paid to this subject when bellows and an oral tube were used. Assisted ventilation in the newborn does not seem to have been used until the 1800s by which time methods for mechanical ventilation in adults were established. Through the 1950s positive and negative ('iron lung' type) pressure devices were tried as were intragastric oxygen, body tilting, phrenic nerve stimulation, and manual bag with mask or tube. Ian Donald and his colleagues, in 1953, were probably the first to use a positive pressure patient cycled respirator in the newborn, but it is strange that, like the early work on penicillin and phototherapy, the significance of their pioneering efforts seemed to go unrecognised. This certainly was the case concerning ventilation in the newborn in the United Kingdom as about another 10 years passed before a paper on assisted ventilation in hyaline membrane disease appeared in the *Archives.*

This 1964 article from Toronto cited reports from only three other centres, one each in a Scandinavian, a South African, and an American journal, from the 11 years between. And even in 1964 it was still considered by many as ethical to use assisted ventilation in only the virtually moribund baby. Not much wonder that out of 18 babies only one survived. Birth weights were given of 12 of those who survived more than an hour of ventilation and they ranged from 1200 g to 3900 g. All but one had a pH below 7·00, a PCO_2 above 100 mm Hg and eight had a carbon-dioxide content below 20 mm/l. The discussion continues:

> 'Infants in the worst condition evinced no appreciable clinical or biochemical response (to ventilation). The necropsy finding of massive pulmonary haemorrhage associated with hyaline membranes explains the failure of assisted ventilation to achieve gas exchange'.
>
> 'It seems that if the stage of clinical death is not too far advanced the condition is potentially reversible'.
>
> 'Our results suggest that the best hope of success with this treatment lies with its application in the pre-terminal rather than in the terminal state'.

Today. With hindsight one could have predicted the high mortality due to very late initiation of ventilation and gross prolonged acid/base imbalance. It is probably hard for younger paediatricians to appreciate that ventilators were, for these reasons and for some considerable time, regarded by many as 'death machines'. Such was the state of the art even in the mid 1960s that it was very difficult to convince the caring team, especially the nurses, that ventilation should be started much earlier in the course of hyaline membrane disease. It is interesting that the massive pulmonary haemorrhages mentioned are now a relatively rare phenomenon, due no doubt to the integrity of the vascular system being maintained by regular biochemical adjustments and to better techniques and controls. Unfortunately, however, other pathologies have taken their place, for example, bronchopulmonary dysplasia, air leaks, and tracheal stenosis.

Thus 25 years on, having passed through the era of the Gregory box and sternal traction we have a new language (PIP, PEEP, IPPV, CPAP) and different uncertainties (synchronous ventilation, paralysis, surfactant, rates, rhythms, and pressures). Let us hope that the encouraging reports about surfactant not only in assisting ventilation but also in reducing the incidence of associated pneumothorax and intraventricular haemorrhage[2] are confirmed and that it will not take us another 25 years to learn how best to use the technology now at our disposal.

References

[1] Goldsmith JP, Karotkin EH. Introduction to assisted ventilation. In: Goldsmith JP, Karotkin EH, eds. *Assisted ventilation of the newborn.* London: W B Saunders, 1981:1–17.

[2] McCord FB, Curstedt T, Halliday HL, McClure G, Reid M McC, Robertson B. Surfactant treatment and incidence of intraventricular haemorrhage in severe respiratory distress syndrome. *Arch Dis Child* 1988;**63:**10–6.

Paul R Swyer, a Londoner, might be regarded as one of the many who made up the 'Brain Drain' after the second world war. The medical 'market' was flooded with demobilised doctors who retrained in all the specialties and for a good many years there was a 'log jam' of senior registrars seeking consultant posts. Professor Swyer, now Emeritus, graduated in 1943 at Christ's College, Cambridge and won the top scholarship to the Middlesex Hospital Medical School. He showed his aptitude for teaching early as a student demonstrator in haematology. He served in the Royal Army Medical Corps in North West Europe and after work at the Brompton Hospital turned to paediatrics in 1949. Like so many others he was enticed to remain abroad in Toronto after a British Council Fellowship there and eventually rose to become Director of Perinatal Medicine and Professor of Paediatrics, University of Toronto.

He is well known for many publications on respiratory and metabolic problems in the newborn, the results of a very active research programme. As author, editor, and reviewer he has made a signal contribution to our knowledge and clinical care of the newborn and through his extensive committee work he has contributed greatly to the organisation of neonatal care in Canada. He has been Visiting Professor in several places in Europe and Scandinavia and was awarded an honorary MD (Lausanne 1984) and a WHO Fellowship in 1985.

Archives of Disease in Childhood, 1989, **64,** 630–639

Correspondence

Treatment of renal failure in neonates

Sir,

Meeks and Sims describe their experiences of acute renal failure in a neonatal intensive care unit; data were abstracted retrospectively from the hospital records over a four and a half year period; and acute renal failure was defined as anuria of 24 hours' duration or concern by a clinician about poor urine output together with a serum urea concentration exceeding 10 mmol/l or serum potassium exceeding 7·5 mmol/l.[1] I would like to comment on some of the points raised in their paper.

Between February and December 1985 I carried out a prospective survey of acute renal failure in 388 consecutive admissions to a regional neonatal intensive care unit. The diagnosis was based on at least one of the following three criteria: a serum creatinine concentration persistently rising over a minimum of two days, oliguria (<1 ml/kg/hour) or anuria resistant to volume repletion and present for a minimum of eight hours, hyperkalaemia (confirmed on a repeat unhaemolised sample; potassium concentration >7·5 mmol/l) together with at least one of the following two criteria: otherwise unexplained metabolic acidosis (pH <7·25, base deficit >10 mmol/l) or haematuria.

Twenty four (6·2%) babies developed renal impairment suggestive of acute intrinsic renal failure; six infants (25%) survived, all of whom had been managed conservatively. Eleven babies presented anuric, 10 oliguric, and three were non-oliguric. Overwhelming septicaemia was the commonest underlying associate, occurring in eight infants (33%), all of whom were of less than 1500 g birth weight. Four babies (17%) suffered severe perinatal asphyxia; all were over 35 weeks' gestation and outborn.

Thirteen of the 24 infants had a plasma urea concentration within the normal range at the time of diagnosis. I would suggest that measurement of plasma urea is of little value in the newborn as it is influenced by numerous nonrenal factors. Misleading rises in the presence of normal renal function may be seen in catabolic states such as trauma and sepsis and in the presence of sequestered blood; conversely, the higher anabolic state of the healthy newborn suggests that relatively smaller increments in serum urea may reflect renal impairment.

The usefulness of three biochemical indices, in the evaluation of the oliguric neonate, was assessed. A fractional sodium excretion exceeding 2·5%,[2] urine to plasma creatinine ratio of less than 20, and urinary sodium concentration exceeding 40 mmol/l,[3] have been described as suggestive of acute intrinsic renal failure. Only 57% of infants with volume repletion resistant oliguria had a fractional sodium excretion of greater than 2·5% however, and 43% a urine to plasma creatinine ratio of less than 20 (poor sensitivity). Although all these infants had a urinary sodium concentration exceeding 40 mmol/l (high sensitivity), the median urinary sodium concentration in infants less than 34 weeks' gestation in the first week of life is around 88 mmol/l (poor specificity).[4]

Retrospective review can only be regarded as a poor index of significant oliguria or anuria. In addition to the possibility of prerenal oliguria, 7% of normal infants fail to void during the first 24 hours of life; neonates do not empty their bladders completely on voiding; sick infants may develop retention of urine. Furthermore the occurrence of non-oliguric renal failure in the neonate is a recognised entity.

Meeks and Sims describe 30 neonates with acute renal failure over a four and a half year period. Though they do not state the total number of admissions over this period, this is likely to be a considerable underestimate, despite their conviction to the contrary. Norman and Assadi reported a 6% incidence of acute renal failure in a series of 314 consecutive admissions to a neonatal intensive care unit[5]; this is a figure similar to ours.

The recognition of acute intrinsic renal failure in the neonate is difficult. Failure to consider the problem in an anticipatory manner, with careful monitoring of urine output and serial measurement of serum creatinine is likely to result in continued underdiagnosis.

References

[1] Meeks ACG, Sims DG. Treatment of acute renal failure in neonates. *Arch Dis Child* 1988;**63**:1372–6.

[2] Mathew OP, Jones AS, James E, *et al.* Neonatal renal failure: usefulness of diagnostic indices. *Pediatrics* 1980;**65**:57–60.

[3] Anand SK. Acute renal failure in the neonate. *Pediatr Clin North Am* 1982;**29**:791–800.

[4] Modi N. Development of renal function. *Br Med Bull* 1988;**44**: 935–56.

[5] Norman M, Assadi F. A prospective study of acute renal failure in the newborn infant. *Pediatrics* 1979;**63**:475–9.

N Modi
Department of Paediatrics
and Neonatal Medicine,
Royal Postgraduate Medical School,
Hammersmith Hospital,
Du Cane Road, London W12 0HS

Drs Meeks and Sims comment:

We read with interest the letter from Dr Modi and would like to reply to some of her comments. Acute renal failure occurred in less than 2% of all admissions to the neonatal medical and surgical units during the study period. Although this figure is much lower than that of other reports,[1] the incidence of acute renal failure depends on the diagnostic criteria used. We assumed oliguria of less than 24 hours' duration to be a feature of hyaline membrane disease rather than acute renal failure.[2] By taking oliguria present for more than eight hours as significant, our incidence of acute renal failure would have been considerably higher, and the survival rate much more favourable.

One of us (AM) has also conducted a prospective study of renal function in babies requiring ventilatory support for four or more days during their first week of life. The study group of 22 babies, mean (SD) gestation 31 (4·3) weeks, represented about 10% of those admitted to the neonatal unit over a six month period and were typical of those requiring intensive care. Depending on the criteria used, the incidence of acute renal failure in the study group was between 5% (hyperkalaemia) and 82% (urinary sodium concentration exceeding 40 mmol/l for 48 hours).

Sick newborns are treated with many drugs having renal effects, such as in this study: frusemide (n=17), isoprenaline (n=6), tolazoline (n=4), epoprostenol (n=3), dopamine (n=2), and sodium nitroprusside (n=1). The natriuretic effect of frusemide, for example, may be delayed until beyond the third day after administration and its duration of action is variable,[3] making interpretation of urinary sodium and fractional excretion of sodium impossible and invalidating their use as parameters for acute renal failure.

We agree that retrospective diagnosis of acute renal failure is far from ideal, but it should be appreciated that prospective recognition may also be difficult. Only by carefully monitoring urine output and critically assessing biochemical parameters will accuracy of diagnosis improve.

References

[1] Norman M, Assadi A. A prospective study of acute renal failure in the newborn infant. *Pediatrics* 1979;**63:**475–9.

[2] Guignard J-P, Torrado A, Mazouni SM, Polin RA. Renal function in respiratory distress syndrome. *J Pediatr* 1976;**88:** 845–50.

[3] Yeh TF, Raval D, Shibli A, Pildes RS. Poor diuretic response to furosemide (F) in small premature infants (<2000 gm) with birth asphyxia. *Pediatr Res* 1974;**18:**367A.

Thyroid function in children after treatment for acute lymphoblastic leukaemia

Sir,

It is known that cranial irradiation during central nervous system prophylaxis of acute lymphoblastic leukaemia can cause endocrine deficiencies, including thyroid dysfunction.[1] Shalet *et al* showed that five out of 58 patients treated for acute lymphoblastic leukaemia had raised serum thyroid stimulating hormone concentrations after treatment with 2400 or 2500 cGy cranial irradiation,[1] and Robison *et al* showed that 10% of long term survivors treated with 1800 or 2400 cGy cranial or craniospinal irradiation had thyroid abnormalities, which included primary hypothyroidism, compensated hypothyroidism, thyroid adenoma, and carcinoma.[2]

In an attempt to discover whether thyroid damage occurs with low dose cranial irradiation, we evaluated thyroid function by measuring concentrations of serum thyroxine and thyroid stimulating hormone in 64 out of 98 patients with acute lymphoblastic leukaemia. They were diagnosed between August 1981 and September 1985 and had received prophylactic treatment to their central nervous systems. The latter comprised 1800 cGy cranial irradiation in 10 fractions over 12 days which was given soon after achieving complete remission and intrathecal methotrexate. All patients were treated according to a protocol devised at this hospital[3] or the UKALL X pilot protocol.[4] The 30 girls and 34 boys were aged between 2 and 12 years (mean 6·2) at diagnosis. Thyroid status was evaluated between three and six years (mean 4·9) from diagnosis.

One out of the 64 children was found to have a mildly raised thyroid stimulating hormone concentration (6·4 mU/l) at three years from diagnosis but this returned to normal within four months. Serum thyroxine concentration was normal when tested on three occasions over this period. The remaining 63 children had normal thyroid function. No patient had clinical evidence of thyroid neoplasia.

A proportion of patients in the study of Robison *et al* received craniospinal irradiation that involved direct irradiation to the thyroid gland. Although they found no association between radiation dose or field and thyroid hypofunction, we surmise that direct irradiation of the thyroid, together with higher dose used in some patients, may account for the increased incidence of thyroid abnormality in their series. None of our patients received irradiation of the spine, and all were treated at the low dose of 1800 cGy. The dose of scattered radiation received by the thyroid gland was assessed in 10 patients and was found to be between 2·5 and 4% of the total dose.

We conclude, therefore, that prophylactic irradiation confined to the cranium at the dose of 1800 cGy is not deleterious to the thyroid gland up to six years from diagnosis.

References

[1] Shalet SM, Beardwell CG, Twomey JA, *et al.* Endocrine function following the treatment of acute leukaemia in childhood. *J Pediatr* 1977;**90:**920–3.

[2] Robison L, Nesbit ME, Sather H, *et al.* Thyroid abnormalities in long-term survivors of childhood acute lymphoblastic leukaemia. *Pediatr Res* 1985;**19:**2566A.

[3] Chessells JM, Leiper AD, Tiedeman K, Hardisty RM. Oral methotrexate is as effective as intramuscular in continuing (maintenance) therapy of acute lymphoblastic leukaemia. *Arch Dis Child* 1987;**62:**172–6.

[4] Pinkerton CR, Bowman A, Holzel H. Intensive consolidation chemotherapy in children with acute lymphoblastic leukaemia (UKALL X pilot)—dose limiting toxicities and supportive care. *Arch Dis Child* 1987;**62:**12–18.

E P Carter
Queen Elizabeth Hospital for Children,
Hackney Road, London E2 8PS

A D Leiper *and* J M Chessells
Departments of Haematology and Oncology,
The Hospital for Sick Children,
London WC1N 3JH

A Hurst
Department of Radiotherapy,
St Bartholomew's Hospital,
London EC1A 7BE

Does ABO incompatibility matter?

Sir,

Quinn *et al* show with the progression from ABO compatibility to ABO incompatibility and then to ABO incompatibility with a positive Coombs test that there is an increasing incidence of jaundice, but the jaundice decreases in severity (see table).[1] About half of the ABO incompatible babies who had a positive Coombs test had a peak bilirubin concentration less than the lower limit of bilirubin in the jaundiced ABO compatible babies

It is clear that jaundice, a positive Coombs test, and ABO blood group incompatibility are not sufficient criteria on which to base a diagnosis of ABO incompatible jaundice. The data are entirely compatible with the assumption that ABO incompatible jaundice is a figment of the paediatricians' vivid imagination.

Reference

[1] Quinn MW, Weindling AM, Davidson DC. Does ABO incompatibility matter? *Arch Dis Child* 1988;**63**:1258–60.

L H P Williams
Victoria Hospital,
Memorial Avenue, Worksop,
Nottinghamshire S80 2BN

Table *Details of infants from Quinn et al*[1]

	Group		
	ABO compatible (control group) (n=110)	*ABO incompatible (n=110)*	*ABO incompatible with positive Coombs test (n=36)*
No (%) with jaundice	18 (16)	29 (26)	14 (39)
Median peak serum bilirubin of jaundiced babies (μmol/l)	190	171	162
Range	159–295	111–282	111–236

Dr Quinn, Weindling, and Davidson comment:

We concur with Dr Williams' interpretation of our data. There is little doubt that bias was introduced into the ascertainment of jaundice because of the paediatricians' prior knowledge of the result of the elution and Coombs test. This would explain increased frequency of detection with lesser severity in elution and Coombs positive cases. We are not sure whether ABO incompatible jaundice is a figment of the paediatricians' imagination or whether the elution and Coombs test are inappropriate for its detection. Brouwers *et al* recently published data suggesting that a combination of the antibody dependent cell mediated cytotoxicity assay and antigen density of A or B antigens on the red cells together provide a good screening test for ABO incompatibility.[1] Unfortunately these investigations are not widely available.

Reference

[1] Brouwers HAA, Overbeeke MAM, Van Ertbruggen I, *et al.* What is the best predictor of the severity of ABO haemolytic disease of the newborn? *Lancet* 1988;ii:641–4.

Rectal nifedipine in acute severe hypertension in young children

Sir,

We read with interest the paper by Evans *et al* on sublingual nifedipine for the treatment of acute severe hypertension.[1] They found that sublingual nifedipine rapidly lowers blood pressure in children with acute severe hypertension and we agree with them.

Evans *et al* did not experience hypertensive children under the age of 5 years.[1] It is difficult to administer a liquid medicine sublingually to young infants. We, therefore, attempted rectal administration of nifedipine in hypertensive children including infants.

The volume inside a 10 mg capsule of nifedipine is 0·34 ml. Based on our dose range (0·2 to 0·5 mg/kg), we aspirated the extra contents from the capsule with a syringe. We made another hole in the capsule which we then administered rectally. We treated nine severely hypertensive children aged 10 months to 15 years,[2] five of whom were under the age of 5. The hypertension was secondary to glomerulonephritis in three, renovascular hypertension in three, and other causes in three. We observed successful effects of rectal nifedipine in all cases, although Evans *et al* failed to control blood pressure in some patients.[1] Its effect in lowering blood pressure appeared within 10 minutes after administration, and lasted more than three hours. Side effects were mild and infrequent; they included asymptomatic tachycardia and mild flushing.

Nifedipine is an excellent drug for the treatment of acute severe hypertension as reported.[1] We are sure that rectal administration is reliable in young children.

References

[1] Evans JHC, Shaw NJ, Brocklebank JT. Sublingual nifedipine in acute severe hypertension. *Arch Dis Child* 1988;**63**:975–7.
[2] Uchiyama M, Hayakawa H, Ogawa T, Hayashi M, Sakai K.

Treatment of hypertensive emergency with nifedipine. *Japanese Journal of Pediatrics* (in Japanese) (in press).

M Uchiyama *and* I Ogawa
Department of Paediatrics,
Medical College of Oita,
Oita 879-56,
Japan

Sublingual nifedipine in acute severe hypertension

Sir,

We read with interest the recent article by Evans and associates in which sublingual nifedipine was shown to be safe and effective for the treatment of acute severe hypertension in children[1]; this is consistent with previous studies. However, van Harten *et al*[2] and McAllister[3] reported negligible sublingual absorption of nifedipine in adults, suggesting that significant nifedipine plasma concentrations are not achieved until the contents of the capsule reach the stomach and are then absorbed. They observed a higher peak nifedipine plasma concentration and a shorter time to reach peak concentrations when a patient bites the capsule to liberate its liquid contents, and then swallows, compared with when they squeeze the contents under the tongue.

Siegler and Brewer reported a mean of 57 minutes (range 15 to 90 minutes) for the time to achieve maximum decrease in blood pressure when nifedipine was administered orally to children while sublingual administration resulted in a mean time to maximum effect of 24 minutes (range 10 to 45 minutes).[4] In this study, nifedipine was administered by the oral route in young patients for whom reliable sublingual administration could not be assured. Thus a possible explanation for the longer time to maximum effect observed in this study with the oral route may be due to pharmacokinetic differences between infants and children. It would be interesting to know the change in blood pressure observed at 15 minutes in the study by Evans and colleagues. This information could then be compared with the onset of action in adults who swallowed the contents of the capsules after biting them and to the onset in infants and children who swallowed the contents of the capsules.

In addition some patients do not tolerate the strong mint taste of the liquid contents of a nifedipine capsule; this can result in nausea and vomiting of the medication. Therefore, in these patients oral administration may be an appropriate alternative as time to peak nifedipine plasma concentrations after oral administration of the capsule in adults appears to occur within 30 minutes.[3]

The data presented by Evans and associates further supports the effectiveness of nifedipine for the purpose of rapidly lowering blood pressure; however, the sublingual route may not be the optimal route of administration in children who can swallow a capsule.

References

[1] Evans JHC, Shaw NJ, Brocklebank JT. Sublingual nifedipine in acute severe hypertension. *Arch Dis Child* 1988;**63**:975-7.
[2] van Harten J, Burggraaf K, Danhof M, *et al.* Negligible sublingual absorption of nifedipine. *Lancet* 1987;**ii**:1363-5.
[3] McAllister RG. Kinetics and dynamics of nifedipine after oral and sublingual doses. *Am J Med* 1986;**81**(suppl 6A):2-5.
[4] Siegler R, Brewer E. Effect of sublingual or oral nifedipine in the treatment of hypertension. *J Pediatr* 1988;**112**:811-3.

R C Hatton *and* M L Marcadis
Department of Pharmacy Services,
Shands Hospital at the
University of Florida,
Gainesville, Florida 32610, USA

Drs Evans, Shaw, and Brocklebank comment:

In our study in those subjects where we recorded values for fall in blood pressure at 15, 30, and 60 minutes after the administration of sublingual nifedipine the maximum fall in blood pressure was seen at 30 minutes.

The mean fall in mean arterial pressure at 15 minutes was 22 mm Hg and at 30 minutes was 32 mm Hg (this excludes values on two non-responders). These results are consistent with the rapid onset of action reported by Siegler and Brewer. However, we fear they do not further our knowledge as to the route of absorption. It may well be that the oral route is preferable (particularly in infants) not because of better absorption but because it produces a slower fall in blood pressure.

Heparin and suspected Sanfillipo syndrome

Sir,

Initial screening of urine from a child with undiagnosed severe learning difficulties suggested a diagnosis of Sanfillipo syndrome. One dimensional electrophoretic separation of mucopolysaccharides[1] from this child's urine showed a large band migrating in the heparan sulphate region (figure). The child had no other features of Sanfillipo syndrome and further urine samples from the same child were normal. Examination of other children, however, from the same school resulted in the fortuitous identification of Sanfillipo A in a previously undiagnosed child.

It seemed unlikely that the original specimen had been collected from the wrong child. It was suggested that the urine sample could have been inadvertently collected into a cytogenetics sample tube. Blood samples for cytogenetic analysis are collected into heparinised 25 ml universal tubes that are otherwise identical to the tubes used by chemical pathology laboratories for urine samples. Repeated analysis of normal urine samples collected into cytogenetics tubes confirmed that the abnormal band originally identified as heparan sulphate was, in fact, heparin.

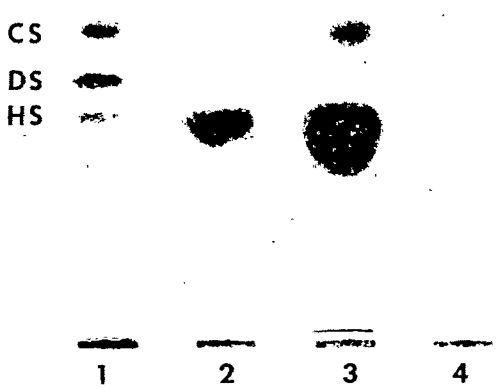


Figure *One dimensional electrophoretic separation of mucopolysaccharides stained with alcian blue. Lane 1: standards: CS, chondroitin sulphate; DS, dermatan sulphate; HS, heparan sulphate. Lane 2: urine collected into cytogenetics bottle; lane 3: urine from a child with Sanfillipo syndrome; and lane 4: urine from a normal child.*

The diagnosis of Sanfillipo syndrome should always be confirmed by white cell enzyme analysis. Heparin contamination is a previously unreported cause of abnormal urine mucopolysaccharide electrophoresis.

Reference

[1] Wessler E. Analytical and preparative separation of acidic glycosaminoglycans by electrophoresis in barium acetate. *Anal Biochem* 1968;**26**:439–44.

M J Henderson, J M McGinlay, *and*
D B Cundall
Departments of Chemical Pathology and
Paediatrics and Child Health,
St James's University Hospital,
Leeds LS9 7TF

Duration of protection against tuberculosis conferred by BCG vaccination in infancy

Sir,

Recent studies confirm that BCG vaccination in the newborn and in infants confers valuable protection against tuberculosis.[1] However, little is known about the duration of protection provided by BCG vaccination. It is often implied that tuberculin skin *sensitivity* induced by BCG vaccination equates with *immunity* provided by BCG, and that sequential tuberculin skin testing therefore gives information about the duration of protection provided by BCG.[2] Nevertheless, there is contrary evidence which suggests that the level of immunity provided by BCG is unrelated to the degree of tuberculin skin sensitivity.[3]

Table *Decreasing effect of BCG with time after vaccination*

Age band (years)	*No of cases*	*Protective efficacy of vaccination (%)*	*95% Confidence interval (%)*
0–3	36	77	53 to 89
4–6	36	60	7 to 83
7–9	21	49	−41 to 82
10–12	15	27	−193 to 92

In order to study the duration of protection provided by BCG we reanalysed the data from a recently published study looking at the effectiveness of BCG given to infant Asian children.[4] In brief, this showed that 57% (62/108) of Asian children who developed tuberculosis had received vaccination, compared with 78% (336/432) of a group of age and sex matched controls who did not develop tuberculosis. The overall protective efficacy of BCG vaccination was 64% (95% confidence interval: 43% to 77%).

The further analysis we undertook consisted of subdividing the cases and controls into four age bands determined by the age at which the cases developed tuberculosis. The proportion of patients and controls within each age band who had received BCG was then ascertained, and the percent efficacy of BCG vaccination calculated as described previously.[4] The table shows the results.

The numbers of cases and controls within each age band were relatively small compared with the overall analysis therefore the 95% confidence interval for each estimate of protective efficacy is wide, and the results must be interpreted with caution. However, the figures for protective efficacy suggest that BCG vaccination in infancy may confer useful protection against tuberculosis for at least nine years after vaccination. More importantly, the maximum protection is provided during the first three years after vaccination—the time when children are at greatest risk from disseminated tuberculosis.

We suggest that the above data reinforce the view expressed in our original publication that BCG vaccination in infant Asians is a valuable protective measure against tuberculosis.

References

[1] Anonymous. Tuberculosis control programme and expanded programme on immunisation. Efficacy of infant BCG vaccination. *Weekly Epidemiology Review* 1986;**28**:216–8.

[2] Grindulis H, Baynham MID, Scott PH, Thompson RA, Wharton BA. Tuberculin response two years after BCG vaccination at birth. *Arch Dis Child* 1984;**59**:614–9.

[3] Tidjani O, Amedome A, ten Dam HG. The protective effect of BCG vaccination of the newborn against childhood tuberculosis in an African community. *Tubercle* 1986;**67**:269–81.

[4] Packe GE, Innes JA. Protective effect of BCG vaccination in infant Asians: a case-control study. *Arch Dis Child* 1988;**63**: 277–81.

G E Packe *and* J A Innes
Birmingham Chest Clinic,
Birmingham

Tubular dysfunction and microalbuminuria in insulin dependent diabetes

Sir,

In a recent paper by Walton *et al* investigating tubular function in diabetics, urinary α-1-microglobulin excretion was found to be significantly higher in diabetic children compared with controls.[1] Using an enzyme immunoassay (Imzyne α_1-M, Fujirebio Inc) we obtained similar results.[2]

In 62 type 1 diabetics (38 girls), aged 3 to 21 years, with duration of disease from one week to 13 years, urinary α-1-microglobulin excretion was evaluated prospectively every three months for one year; 54 healthy subjects (32 girls), aged 4 to 21 years served as controls. Diabetics were divided into three groups according to their duration of disease (group A: less than five years; group B: five to 10 years; group C: more than 10 years); during the study 28 poorly controlled children (with stable glycated haemoglobin (HbA_{1c}) concentration >10%) improved their metabolic control and after 12 months HbA_{1c} concentrations were less than 8%. In diabetics urinary excretion of α-1-microglobulin was significantly higher than in controls, particularly in group C patients. In agreement with Dr Walton's study, a significant correlation was found between HbA_{1c} values and urinary α-1-microglobulin excretion as well as between 24 hour glycosuria and urinary excretion of α-1-microglobulin. In poorly controlled diabetics with duration of disease shorter than 10 years (group A and B) urinary α-1-microglobulin excretion returned to normal when metabolic control improved, while it remained high in children with duration of diabetes longer than 10 years (group C) (table). Albumin excretion rate was less than 15 µg/minute in all diabetic children during the study.

Table *Urinary α-1-microglobulin excretion (mg/mmol creatinine) in 28 poorly controlled diabetic children and in 54 normal children*

	During poor glycaemic control (stable HbA_{1c} >10%)	*After 12 months of improved metabolic control (HbA_{1c} <8%)*
Diabetic children:		
Group A (n=9)		
Median	0·54*	0·27
Range	0·21–1·64	0·11–0·94
Group B (n=10)		
Median	0·62*	0·29
Range	0·18–1·78	0·16–0·96
Group C (n=9)		
Median	0·75*	0·66*
Range	0·28–2·07	0·22–1·98
Normal children		
Median	0·25	
Range	0·10–0·88	

*p<0·001 compared with normal children.

Our data confirm that glycaemic control influences urinary excretion of α-1-microglobulin; however, despite good metabolic control, children with long duration of diabetes and without microalbuminuria show an increased excretion of α-1-microglobulin.

Although diabetic kidney disease is primarily a glomerulopathy,[3] we believe that impaired tubular function is detectable earlier than glomerular damage.

References

[1] Walton C, Bodansky HJ, Wales JK, Forbes MA, Cooper EH. Tubular dysfunction and microalbuminuria in insulin dependent diabetes. *Arch Dis Child* 1988;**63**:244–9.
[2] Chiarelli F, La Penna G, Anichini M, Morgese G. Urinary excretion of α-1-microglobulin in children with type 1 (insulin-dependent) diabetes mellitus. *Pediatr Res* 1987;**22**:218.
[3] Mackintosh D, Viberti GC, Keen H. Proteinuria in diabetes. *Diabetologia* 1983;**24**:304.

F Chiarelli, G La Penna, *and* G Morgese
University Department of Paediatrics,
Ospedale Pediatrico,
I 66100 Chieti, Italy

Bulging fontanelles in infants without meningitis

Sir,

We read with interest the article by Mann *et al* on transient intracranial hypertension of infancy.[1] We submitted a similar report to this journal in 1986 that was not accepted for publication in competition with other papers coming through at that time.

Over a six year period, seven infants (see table) were admitted to the Royal Alexandra Hospital for Sick Children, Brighton, with bulging fontanelles and fever. Examination of the cerebrospinal fluid and blood cultures was normal in each case. All seven were previously healthy, but case 4 had Poland's anomaly. Cerebrospinal fluid pressure was raised in the three infants who had the investigation performed. All the infants' fontanelles had returned to normal within 72 hours. We believe all our patients were suffering from viral infections, but the relevant investigations were not complete. A history of mild head injury was obtained in case 3. In two of our cases the bulging fontanelles returned in the presence of further infections. The mother of case 4 brought her daughter back

Table *Details of infants with bulging fontanelles*

Case No	*Sex*	*Age (months)*	*Symptoms*	*Cerebrospinal fluid pressure (cm H_2O)**	*Cerebral imaging*	*No of recurrences*
1	F	5	Upper respiratory tract infection	Not done	Not done	—
2	M	4	Upper respiratory tract infection	30–32	Computed tomogram, normal	—
3	F	9	Upper respiratory tract infection	30	Ultrasound normal	1
4	F	4	Gastroenteritis (Echo 18 virus)	16	Ultrasound normal	2
5	M	5	Febrile, rash over shoulders	Not done	Not done	—
6	M	4	Gastroenteritis	Not done	Not done	—
7	F	2	Upper respiratory tract infection	Not done	Not done	—

*Normal range for infants 4–15 cm H_2O.[3]

to the hospital twice with recurrences of her bulging fontanelle, and at a later date admitted that her fontanelle became distended whenever she developed a cold.

There have been few other reports of this phenomenon. Amacher and Spence reported on a 15 month old boy with similar findings in a review of 23 cases of benign intracranial hypertension in childhood and adolescence.[2] Of those under 12 years, 50% had a viral aetiology, and over half did not have papilloedema. Papilloedema was not seen in any of our cases. The normal computed tomography and ultrasound results were in keeping with the diagnosis. All the scans by Amacher and Spence were normal, save for two in whom the ventricles were small.

The patients in our series remained surprisingly well. Apart from the two who had gastroenteritis, only two of the remaining five were vomiting. In addition to the infants in this report, three others have been seen with bulging fontanelles after respiratory infections. Lumbar punctures were not performed as the infants were recovering when seen. It is tempting to speculate that the fontanelle acts as a 'safety valve'. Perhaps the phenomenon has been under recognised because infants have fewer symptoms associated with raised intracranial pressure than adults who have rigid skull vaults.

References

[1] Mann NP, McLellan NJ, Cartlidge PHT. Transient intracranial hypertension of infancy. *Arch Dis Child* 1988;**63**:966–8.

[2] Amacher AL, Spence JD. Spectrum of benign intracranial hypertension in children and adolescents. *Childs Nerv Syst* 1985;**1**:81–6.

[3] Belton NR. Biochemical and physiological tables and function tests. In: Forfar JO, Arneil GC, eds. *Textbook of paediatrics.* 3rd ed. Edinburgh: Churchill Livingstone, 1984:1977–2007.

W Barry, W Lenney, *and*
G Hatcher
Royal Alexandra Hospital for
Sick Children, Dyke Road,
Brighton BN1 3JN

The Family Fund

Sir,

Paediatricians have supplied reports to the Family Fund for many years in support of families of severely disabled children. About 105 000 families have benefited since 1973.[1] Washing machines, dryers, and holiday relief are the most needed and the present budget is £8 million of government money.

Recently the Fund has been unable to help the parents of two of my patients (the only children of the family). They are severely mentally retarded, undiagnosed with marked involuntary movements, have very little independent mobility, and severely limited communication at the ages of 5 and 7 years. The Fund accepts that the children's disabilities come within its medical criteria but is unable to offer the family help on the grounds that their economic circumstances do not justify it.

The Fund reports that only 0·9% of families have been refused help on the grounds that 'they are too wealthy' for the purposes of the Fund. It also accepts that parents who are denied on these grounds feel angry, and observes that all families tend to live up to the edge of their income: 'Relatively well off families have understandably high expectation in material and personal terms so that the stress they experience can be no less acute than that experienced in less favourable circumstances'.[2] The Fund stresses that it does not operate a means test but justifies each grant individually. It comments on its sensitivity to the exceptional expense of having more than one handicapped child, or unusual expenses because of particular disabilities.

The Family Fund grew out of the appreciation of the cost of caring for disabled children after the thalidomide tragedy,[3] and it is accepted that low income families should have greatest priority.

If my patients' families were 'wealthy' in the ordinary sense of the term, this letter would not have been written. 'Too wealthy' is a threshold under regular review but seems to be around a gross income of £12 500 per annum.

Admittedly a quarter of all children in Britain have no annual holiday (half in Manchester). One in 20 has no washing machine (15% in Manchester). And there are families with quite limited incomes who fund holidays and laundry equipment. But if children meet the medical criteria for severe disability should there be exclusions at such moderate levels of income? If so, applications should be discouraged.

References

[1] Bradshaw J, Lawton D. 75,000 severely disabled children. *Dev Med Child Neurol* 1985;**27**:25–32.

[2] Barnes EM. *The Family Fund and how it helps*. 2nd revision. York: The Ebor Press, 1988.

[3] Baldwin S. *The cost of caring*. London: Routledge and Kegan Paul, 1985.

I A McKinley
Royal Manchester Children's Hospital,
Pendlebury,
Manchester M27 1HA

Transient neonatal galactosaemia

Sir,

The case reported by Taylor *et al* reminds me of a child I saw in 1980 with a similar syndrome in association with cystic fibrosis.[1]

Case report

A first born girl was admitted to hospital at the age of 3 months because of failure to thrive (birth weight 3100 g, admission weight 3900 g: less than the third percentile). There were no specific clinical abnormalities. She was anaemic with a haemoglobin of 80 g/l and a reticulocyte count of 13%. She had abnormal liver function tests with a low plasma albumin concentration of 25 g/l and a raised serum glutamo-oxaloacetic transaminase activity of 169 IU/l. Tests for bleeding, jaundice, congenital infection, hepatitis B antigen, and α_1 antitrypsin deficiency gave negative results. Her urine contained galactose and a plasma galactose concentration was 5·8 mmol/l (upper limit of normal 0·24 mmol/l). Subsequently red cell enzymes were studied and she was shown not to have deficiencies of galactose-1-phosphate uridyl transferase, galactokinase, or epimerase.

She was treated with a galactose free diet, and galactose concentrations were normal within three days. She thrived so that her weight achieved the 10th percentile at 6 months of age and her liver function returned to normal. At 9 months a milk diet was reintroduced and her urine remained galactose free. She was admitted to hospital at the age of 3 years because of weight loss and pneumonia. Sweat sodium concentrations were 84, 88, 117, and 115 mmol/l. She has responded well to treatment for her cystic fibrosis.

Comment

This case is very similar to that reported by Taylor *et al.* The response to a galactose free diet suggests that her liver abnormality was secondary to the raised blood galactose concentration. There were no clinical stigmata of cystic fibrosis before admission at the age of 3 years with chest symptoms and weight loss. Though cystic fibrosis may be associated with neonatal jaundice, this had not occurred.

Reference

[1] Taylor CJ, Rattenbury JM, Allen JC, Tulloh R. Transient neonatal galactosaemia. *Arch Dis Child* 1988;**63**:1388–90.

C H Cheetham
Amersham General Hospital,
Amersham, Bucks HP7 0JD

Sudden death in incomplete Kawasaki disease

Sir,

We read with interest the case report by McCowen and Henderson regarding sudden death in incomplete Kawasaki disease.[1] Recently we managed a similar patient presenting with this syndrome who died suddenly despite a normal echocardiogram.

A 2 year old Asian girl was admitted with a six day history of fever and four days of rash. The rash was maculopapular, starting on the chest and spreading to the limbs. She had mild palmar erythema, cervical lymphadenopathy, stomatitis, and mild hepatomegaly. On admission the erythrocyte sedimentation rate was 125 mm in the first hour. The C reactive protein was 83 mg/l and the platelet count was 448×10^9/l rising to 762×10^9/l on the eighth day after admission. Cross sectional echocardiography confirmed normal ventricular dimensions and function. The proximal coronary arteries were well visualised and were of normal calibre. The electrocardiogram was also normal. Bacterial cultures and viral serology were negative, serum immunoglobulins, complement and antistreptolysin O titres were normal. Neutrophil cytoplasmic antibodies were not present. On the ninth day in hospital her temperature settled and she was clinically improved. There was desquamation of the truncal rash, but not of the fingers. Forty eight hours later the patient collapsed suddenly and could not be resuscitated.

At necropsy the right coronary artery was occluded by recent thrombus close to its origin. The wall of the left anterior descending branch was thickened and the lumen narrowed. Histology showed coronary arteritis without aneurysmal dilatation.

Children with Kawasaki disease who have a high risk of developing coronary complications are Asians, aged less than 5 years, with fever longer than 14 days, and high erythrocyte sedimentation rates and platelet counts.[2 3] This case illustrates the limited predictive value of echocardiography in the acute stage with regard to cardiac complications. It also raises the question of when to institute antiplatelet treatment in children presenting with fever, a rash, and thrombocytosis.

References

[1] McCowen C, Henderson DC. Sudden death in incomplete Kawasaki's disease. *Arch Dis Child* 1988;**63:**1254–6.

[2] Japan Kawasaki Disease Research Committee. *Diagnostic guideline of Kawasaki disease.* Revised edition 4. Tokyo: Japan Kawasaki Disease Research Committee, 1984.

[3] Ichida F, Fatica NS, Engle MA, *et al.* Coronary artery involvement in Kawasaki syndrome in Manhattan, New York: risk factors and role of aspirin. *Pediatrics* 1987;**80:**828–35.

M D LOUBSER, M C HOH, *and* N SREERAM
Children's Department,
Newcastle General Hospital,
Westgate Road, Newcastle upon Tyne
NE4 6BE

Late onset ornithine carbamoyl transferase deficiency in males

Sir,

We were interested that Drogari and Leonard did not mention sodium valproate as a possible precipitant of symptoms in late onset carbamoyl transferase deficiency in males.[1] We wish to report such a case; to our knowledge this has not been reported before.

A 10 year old boy, who had no previous medical or family history, was started on sodium valproate 200 mg twice a day for worsening photosensitive absence seizures. After three weeks a subtherapeutic concentration of the drug prompted an increase in dose to 200 mg three times a day. Five days later the boy vomited twice. Solids and sodium valproate were withheld. The next day he vomited three more times and became difficult to rouse in the general practitioner's surgery. He was immediately admitted to hospital but remained easily rousable overnight. Twelve hours after admission his conscious level deteriorated. Blood glucose concentration was 5·5 mmol/l and ammonia 145 μmol/l, his prothrombin ratio was 1·5 and aspartate aminotransferase activity 47 IU/l. All other liver function tests and a computed tomogram were normal. Blood sodium valproate concentration was 0 16 mg/l (subtherapeutic).

Eighteen hours after admission he was transferred to another hospital for intensive care. Assisted ventilation was begun. Intracranial pressure was low initially. Thirty six hours after his first hospital admission the blood ammonia concentration was 245 μmol/l and intracranial pressure 2·67–4·00 kPa. Chromatography of the urine showed a peak of orotic acid. This was initially a very small peak but after reversal of the effect of sodium valproate with sodium benzoate, became a very large peak typical of ornithine carbamoyl transferase deficiency. Despite aggressive management of his intracranial pressure and appropriate doses of dextrose, sodium benzoate, arginine, and growth hormone, intracranial pressure rose to 7·33 kPa and ammonia to 918 μmol/l over the next 12 hours before coming under control. His cerebral perfusion pressure could not subsequently be maintained and he died on the sixth hospital day. Very low residual ornithine carbamoyl transferase activity of 1·6 μmol/mg/hour (and normal carbamoyl phosphate synthetase activity) was confirmed in liver obtained immediately postmortem.

Hyperammonaemia and brain swelling in valporate toxicity complicating urea cycle disorders are more often rapidly progressive and fatal than in classical Reye's syndrome even if, as in the present case, early and aggressive treatment is given. Such deaths are one of several metabolic hazards of sodium valproate that must be weighed against the potential benefit of treatment.[2]

References

[1] Drogari E, Leonard JV. Late onset ornithine carbamoyl transferase deficiency in males. *Arch Dis Child* 1988;**63:**1363–7.

[2] Brown JK. Valproate toxicity. *Dev Med Child Neurol* 1988;**30:** 121–5.

C R KENNEDY *and* J J COGSWELL
Department of Child Health,
Southampton General Hospital,
Shirley, Southampton SO9 4XY

Rubella immunisation for girls over 14 years

Sir,

I was interested to read Dr Hodes' article on rubella immunisation for girls over 14 years,[1] but believe that her findings may not justify her recommendation that rubella vaccination should be offered to girls until they leave school at 16 years of age.

Dr Hodes offered her programme to 56 of 83 girls whose rubella immunity status was unknown, but she does not tell us why the other 27 were not invited. Only 25 of the 56 accepted, and 21 of them (84%) were found to be seropositive. The other four were vaccinated. The increase in the proportion of girls vaccinated or immune from 86% to 90% was due largely to the finding of seropositive girls, and much less to vaccination.

If it is assumed that the same proportion (84%) of all 83 girls was immune, 566 girls (96·6%) were vaccinated or immune before Dr Hodes' programme was introduced, and 570 (97·2%) afterwards. While applauding every effort to increase rubella immunity in the community, I wonder whether this marginal increase justified the expense of the enterprise.

Reference

[1] Hodes D. Rubella immunisation for girls over 14 years. *Arch Dis Child* 1988;63:983–5.

R W SMITHELLS
University Department of Paediatrics and Child Health,
Leeds General Infirmary,
Belmont Grove, Leeds LS2 9NS

Dr Hodes comments:

Professor Smithells rightly criticises the fact that only 56 of the 83 eligible girls were invited. This was due to many practical problems that were described in the second and third paragraphs of the discussion. This is a shortcoming of the study and in future one would have to try harder to invite all eligible girls.

Assuming that the same proportion (84%) of all 83 girls was immune, 70 girls would be seropositive and 13 seronegative. The total number of girls vaccinated or immune would have been (503+70) 573 (97·8%) before the programme and (573+4) 577 (98·5%) afterwards. Professor Smithell's figures of 566 and 570 respectively are probably due to an inadvertent miscalculation. In other words, there were 13 (2·2%) seronegative girls before and nine (1·5%) after the programme. The vaccination of four girls is worth the estimated cost of at most a few hundred pounds. There are still 20 cases a year of congenital rubella syndrome.[1] Until rubella disease is eliminated it is extremely important to achieve an uptake of 100% in women of child bearing age. If the study had been completely succesful all 13 girls would have been vaccinated.

Reference

[1] Joint Committee on Vaccination and Immunisation. *Immunisation against infectious disease.* London: HMSO, 1988.

Reflex anal dilatation associated with severe chronic constipation in children

Sir,

Reflex anal dilatation is an important sign associated with anal abuse in children.[1] The buttocks are parted gently and the examiner waits for up to 30 seconds. Where the sign is present, the anal sphincter dilates to up to 2–3 cm and a view of the interior of the rectum is observed. The anus then frequently closes and then reopens in a dynamic fashion.

Dr Clayden describes a 'visibly relaxed anus such as one sees when a large faecal mass has chronically distended the rectum leading to a sphincter which is dilated'—there is no suggestion of the dynamic findings of reflex anal dilatation described in his paper.[2]

Perhaps if doctors could agree a common vocabulary,[1] then these kind of irrelevant disagreements would not exist.

References

[1] Butler-Sloss E. *Report of the inquiry into child abuse in Cleveland 1987.* London: HMSO, 1988.
[2] Clayden GS. Reflex anal dilatation associated with severe chronic constipation in children. *Arch Dis Child* 1988;**63**:832–6.

C J Hobbs *and* J M Wynne
St James's University Hospital,
Beckett Street,
Leeds LS9 7TF

Archives of Disease in Childhood, 1989, **64,** 640–642

Book reviews

Programmes to Promote Breastfeeding. Edited by D B Jelliffe and E F Patrice Jelliffe. Pp 490: £30 paperback. Oxford University Press, 1988. ISBN 0-19-261457-6.

Is the pendulum swinging back towards professional backing for breast feeding? I write this in the week before the vaccine for measles, mumps, and rubella erupts and have the feeling that paediatricians are fully behind this campaign. Our enthusiasm for breast feeding seems to have been less thunderous and perhaps this is one reason why fewer mothers are breast feeding.[1] The Jelliffes' latest book, together with the forthcoming national campaign in the United Kingdom, may spur us to better things.

The editors have gathered a galaxy of 85 international experts on breast feeding and therefore there is a degree of overkill. The book looks at small scale and national programmes, the role of support groups, international agencies and professional associations (Canada, the United States, and Scandinavia are the stars—poor marks for the United Kingdom), at the role of the health service and the market, and at training and 'policy issues' (including the state of the WHO Code in each country). It is almost inevitable that when so many authors are writing on a subject close to their heart that there will be much rhetoric and repetition. Had the essence of the successful programmes been distilled into 100 pages I believe we would have a best seller. A major defect is the lack of differentiation between campaigns in developed and developing countries. Though we can learn from the latter, the dangers of bottle feeding are far less in industrialised countries hence the thrust of the argument must be more on allowing informed choice than on the public's health. What then are the keys to successful promotion? I can only pick out a few, noting with interest that measures targetted at health care workers, hospital practices, and the legislative field worked better than programmes aimed at teaching mothers.

In the Phillipines, Dr Clavano revolutionised hospital practice and reduced infections by phasing out milk formula and bottle feeding completely in postnatal wards. In Finland, babies were put to the breast after birth and supplementary feeding was abandoned: in 1983, over 90% of babies breast fed for over three months. Canadian paediatricians organised a national information service for physicians and hospital staff. Photographs of staff breast feeding their babies were posted in an antenatal clinic in Mexico. The best example of successful legislation to control bottle feeding is Papua New Guinea, which put feeding bottles on prescription only in 1977, with dramatic reduction in malnutrition and gastroenteritis.

Can we learn from this book? It should certainly be to hand in all maternity and neonatal units. More important perhaps is to use it as an incentive for the BPA's soon to come breast feeding campaign?

Reference

[1] DHSS. *Present day practice in infant feeding.* 3rd Report. London: HMSO, 1988.

A J R Waterston
CONSULTANT PAEDIATRICIAN
Newcastle General Hospital,
Newcastle upon Tyne

Clinical Nutrition in Paediatric Disorders. By D Bentley and M Lawson. Pp 332: £42·50 hardback. Baillière Tindall, 1988. ISBN 0-7020-1245-9.

'Including digestion without tears for jobbing paediatricians' might have been a suitable subtitle, as it describes the authors' intentions. A collaboration between a paediatrician and dietician, the result is an interesting hybrid. The first 197 pages are devoted to pathophysiology, clinical aspects, and management. The appendices run to 107 pages, possibly meriting an entry in the *Guinness Book of Records* for a work of this length. Clearly the aim is to present the relevant dietetic data without rendering the main text indigestible. In this it succeeds admirably.

The first clinical section deals with normal nutritional needs, dehydration, parenteral and enteral nutrition, and malnutrition. It also contains sections on nutrition in cancer, burns, and trauma. The second section is a conventional ramble through gastrointestinal and hepatic disorders, and the third deals with nonenteric disorders requiring modified diets for cardiac and renal disease, diabetes mellitus, obesity, and anorexia.

Each topic is introduced by a mini review of current trends, suitably laced with up to date references. A description of the pathophysiology, a list of major features and investigations precede diagnosis and treatment. One criticism: research and esoteric investigations, although of interest to the paediatrician, are lumped together with the more established and proved tests, without at times giving clues as to relative usefulness, reliability, or practicality.

The text is replete with tables, figures, and diagrams that seek to break down the barriers to understanding the intricacies of digestion.

The appendices are to be used as companions to the text, and marshall together a great deal of information from national and international recommended dietary intakes and manufacturers' data. More worked examples would have helped my understanding. Overall, worth a read as a more practical approach than the standard texts, with a user friendly, not entirely 'cookbook', approach. I am sure it will find a place in many paediatric departments.

A Habel
CONSULTANT PAEDIATRICIAN
West Middlesex University Hospital

Pathogenesis and Immunity in Pertussis. Edited by A C Wardlaw and R Parton. Pp 482: £55 hardback. John Wiley, 1988.

This must be the most definitive work on this subject available at the present time. It is not a book for the shelves of most general paediatricians but more a reference book that is likely to be seen on the shelves of microbiologists.

This book brings the combined knowledge of 31 authors, from six countries, together in 21 chapters. It is written predominantly by microbiologists, and covers all aspects of the organism and the disease. The early chapters cover the growth and virulence and the mechanism of action of each of the toxins. Further chapters consider the clinical aspects of pertussis, rological responses, and the host parasite lationship. The final chapters review the ficacy and reactions to both whole cell nd acellular vaccines and their impact on e epidemiology of the disease.

I found the book remarkably easy to read for a non-microbiologist and this is largely due to the concise editing and clear format particularly of the content pages. It is both well indexed and referenced.

It makes interesting reading but it is more a reference book and with this in mind I will be donating this review copy to the local postgraduate library.

S Lenton
COMMUNITY PAEDIATRICIAN
Bath District Health Authority

The Practical Assessment and Management of Children with Disorders of Development and Learning. By Mark L Wolraich. Pp 471: £30·50 paperback. Wolfe Medical Publications, 1988.

This book has been written for American primary care physicians, consequently it is difficult to suggest an audience in Britain whose needs it would meet. Too detailed for the general practitioner, it gives both too little and too much information on some topics for the paediatrician. The title is misleading; the emphasis throughout is theoretical and the reader looking for 'how to do it' guidance will be disappointed. The preface defines the scope of the text as 'behavioural pediatrics' and there is a confusing inclusion of topics that could be considered the province of child psychiatry, at the expense of more detailed discussion of developmental disorders and handicapping conditions.

The book follows a common format, the first section dealing with techniques of assessment and management and the second covering specific disorders. This inevitably results in discussion of some complex disabilities in insufficient detail for the paediatrician. There are some good general chapters and I appreciated the emphasis on the need for a family centred approach. The detailed chapters on methods of assessment, however, were less useful in their extensive consideration of tests not in general usage in the United Kingdom. The chapters on speech and language disorders are disappointing and important omissions are chapters on neurological examination, genetic counselling, and clinical tests of vision and hearing.

Management recommendations reflect the pattern of services in the United States—no references to district handicap teams but, thankfully, the verb 'to statement' has not yet crossed the Atlantic. Inevitably, a book on developmental disorders must be written in the context of the services, professional structures, and economy in which its readers work. Although there are some good sections, this book will not find a ready market in Britain.

S Ilett
CONSULTANT COMMUNITY PAEDIATRICIAN
Community Services Unit,
Birmingham

Neonatal Respiratory Care. Edited by W Carlo and R Chatburn. Pp 474: £22·50 hardback. Year Book Medical Publishers, 1988. ISBN 0-8154-5636-7.

This deceptively small volume is the second edition of a book originally produced in the late 1970s, with an authorship mainly from Cleveland, Ohio. It presents the reader with a holistic approach that covers most aspects of neonatal intensive care and the embryological development of the respiratory system. This reflects the sick newborn's multisystem disease from which it is difficult to separate one organ system.

The first quarter of the book concerns development, structure, and physiology of the respiratory system, which in the main is comprehensively executed. Many of the illustrations will be familiar to readers from standard texts. The second quarter deals with clinical aspects, ranging from delivery room management and nursing care to pharmacology and care of the parents. In many ways this section is the least satisfactory. Although it covers important areas of neonatal care, one sometimes feels that the relevance to respiratory care is lost in more general discussions. It is also rather repetitive, for example there are three descriptions, in separate chapters, of how to pass an endotracheal tube, including two different guides to endotracheal tube size. Much of this is further covered in the chapter on nursing care, which again is not specifically respiratory care.

Because of the space devoted to clinical aspects the chapters covering respiratory diseases, radiology, and complications are relatively brief. Despite many recent references, these rarely stray from the North American literature and ignore important recent papers. The concluding chapters cover ventilation, including descriptions of high frequency ventilation, extra corporeal membrane oxygenation, and other new modes of gas exchange. Finally an appendix brings together a huge amount of normative data from multiple sources.

Despite its comprehensive coverage of the subject, this book will be most useful to the paediatrician in the United Kingdom for the reference value of its outer chapters and appendices. It joins a fiercely competitive group of texts dealing with neonatal respiratory illness.

N Marlow
LECTURER IN CHILD HEALTH
Royal Liverpool Children's Hospital

Recent Advances in Epilepsy. Edited by Timothy A Pedley and Brian S Meldrum. Pp 266: hardback £45. Churchill Livingstone, 1988.

Epilepsy is the commonest chronic neurological disorder of childhood. Advances in the understanding of underlying mechanisms, investigation, and treatment are the remit of general as well as specialist paediatricians.

In this, the fourth of their series, the editors have maintained the very high standard previously achieved. All those who request electroencephalography should read the chapter on the role of the electroencephalogram in the diagnosis and management of epilepsy. There are discussions on how to obtain the maximum information from the record, where it may be helpful in the choice of therapy, and its roles in long term follow up and withdrawal of treatment. For those who follow their patients into adolescence, and for the neonatologists, teratogenic aspects of antiepileptic drugs are considered in detail. Epilepsy presenting as a symptom of parasitosis may not be very common, but the coverage of the neurological complications of parasitic infestations is wide and gives access to much literature published in languages other than English. Prospects for improvement in seizure control by the introduction of new drugs are considered with admirable clarity. There is a detailed analysis of the place of corpus callosotomy for intractable secondary generalised seizures. The contributions on kindling; initiation and neuroanatomical spread of seizure activity; and, amino acid abnormalities in plasma, cerebrospinal fluid, and brain are clearly written and well referenced, but the clinician may find them rather too theoretical.

For the general paediatrician there is much in this volume to help in the day to day management of epilepsy. For the specialist in childhood epilepsy there is an imaginative range of contributions, and all are superbly referenced.

S J WALLACE
CONSULTANT PAEDIATRIC NEUROLOGIST
University Hospital of Wales, Cardiff

Biology of Human Milk. Edited by Lars A Hanson. (Nestlé Nutrition Workshop Series Vol 15.) Pp 231: $61·50 hardback. Raven Press, 1988. ISBN 0–88167–431–1.

With so much discussion concerning the suitability of formula milks particularly for the low birthweight neonate, it is encouraging to find a book devoted to the opposition! This book represents the latest in the *Nestlé Nutrition Workshop* series and has pulled together experts from both Europe and the United States and represents a broad depth of investigation.

The subjects covered are the chemical composition of human milk, from protein to the trace elements, both the hormonal factors and enzymes present and their possible roles, and the anti-infective properties, including cellular as well as chemical constituents. The style is to give an authorative view, and then to include discussion from the participants at the workshop, which generally works well, and many of the important points raised occur in the discussion sections, which add depth to the book.

The subjects covered are, in the main, well chosen, and provide an idea of p gress for those not in the field of rece advances in the study of breast milk. It disappointing, however, that so litt mention is made of practical problems th present themselves to those concerned wit feeding sick infants, and in particular th role of milk banking. With so muc concern about HIV and breast milk, found it surprising that this only warrante a couple of lines in discussion.

On the whole this is a fascinating book, and while there is little to be gaine practically, it does give an insight into th gold standard for infant nutrition, and such should be read by those responsib for infant feeding.

N MEADO
CONSULTANT PAEDIATRICIA
Whipps Cross Hospit

Archives of Disease in Childhood, 1989, **64,** 643–645

National Health Service White Paper

Will it work for patients?

Repeated attempts to reorganise the National Health Service (NHS) have in the past concentrated on the differing layers of consensus, management, and varying sizes of the administrative unit. Paediatricians have continued to 'manage' their clinical services for children without adequate information and no control over or knowledge of the resources available to them. They have had to face a continuing shortage of manpower and aging and inadequate facilities against the background of increasing demands being made upon them. The Government's White Paper *Working for Patients* with its eight satellite working papers is a fundamental and radical rethink which will have a direct effect on our everyday professional lives and the way we care for our patients. The Government has set itself two objectives: (1) to give patients, wherever they live in the United Kingdom, better health care and greater choice of the services available; and (2) to give greater satisfaction to those working in the NHS who successfully respond to local needs and preferences. The quest for value for money 'must be an essential element' and those who take decisions which involve the spending of money must be accountable for them.

Internal markets

To achieve greater choice the Government are to establish an internal 'provider' market for hospital services. The district health authorities and budget holding general practices of over 11 000 patients will act as 'commissioning' authorities with individual hospitals: self governing Trust Hospitals, the district managed hospitals, and independent hospitals who would compete with each other as 'providers'. All general practitioners will be informed of the hospitals with which the district health authority has entered contracts and the nature of these contracts. They will be expected to refer patients within the terms of the contract and to those hospitals or departments which (in the district's view) offer the best 'value for money' care.

This internal market will require a much more sophisticated information system than is currently available. It will also require more accountants and a new breed of lawyers to advise about how contracts will work and what to do if they fail. The Government recognises the need for 'better information' and has committed itself, in advance of the agreed evaluation by the profession due to be conducted this October, to the Resource Management Initiative (RMI). This initiative involves doctors, nurses, and other professional staff having information 'at their fingertips' about the care that their patients are getting. This is a welcome goal. But the information system needs to be 'patient' based and available on computer 24 hours a day seven days a week. It will cost a lot of money which must not come from the existing patient services. Unless such an operational system is sound and reliable, serious and costly errors by management will result as they do now from inaccurate, out of date, narrow based and irrelevant information. Before embarking on any responsibility for managing their clinical resources, paediatricians must be confident in their information system for children's services.

Funding

The central funding of the NHS will be cash limited by Parliament. The resource allocation working party formula is to be revised rather than discontinued. The formula is already based on populations adjusted for standardised mortality ratios. These ratios are still to be used as a morbidity measure for death rates to people under the age of 75. The new feature added to the formula will be the cost of providing services. The problem with paediatrics is that child mortality being low is not a good indicator of child morbidity, which is relatively high. The new formula will still not take into account the social factors in a population which have a major impact on child morbidity. The Government has recognised that 'sudden and substantial change' in the money available for services in a district population would occur if the revised Resource Allocation Working Party (RAWP) formula, originally designed for regional populations, was to be applied immediately to each health district. Children's services would be particularly susceptible to such swings. On the other hand paediatricians will be able to price the child health services more accurately in the future and therefore make an improved, well thought out, and supported case for the provision of additional services by the identification of local needs. The imposed central formula from above is likely to cause a cash clash between the operational data available at local level.

District services

Two other important principles have emerged from the White Paper working papers. Firstly, each health district will 'open its account in a position at least to continue to provide health care at the level which that population has enjoyed' and that secondly 'emergency' treatment should always be immediately available and without question. The majority of hospital paediatrics involves emergencies but the child health services which provide preventive developmental education and social paediatrics are non-acute but have considerable impact on the 'acute' services. It is thus essential that an appraisal of the existing services provided in each district is made so that they at least are not compromised and that information is developed on which the service can be improved. Some definition of what comprises an emergency will be necessary.

Districts are to identify their own 'core' services. Core services are those that must be provided locally. They include accident and emergencies and central public health services. The existing guidelines refer indirectly to the maternity services but not specifically to paediatrics and child health. It is essential that the services for children both in acute hospital departments and in the child health services are locally available. Otherwise the services for children will disintegrate. Each health district must have a fully staffed acute children's unit in association with a maternity department.

There are opportunities in the White Paper for 'community services' to merge with hospital services. Paediatricians should seize on these in order to achieve full integration of the services for children in their districts. By joining together they will be able to make better use of their combined resources and it would be timely if the British Paediatric Association could issue some guidance to their members and health authorities about how this could be implemented. The danger to the community child health service lies in the lack of information about their activities particularly with regard to their support of the education authority and the social services. Health service indicators abound for acute care but there are very few for the 'community'. Those that exist are very narrow based. Managers therefore could cast a blind eye and cut services without any discernible effect on those health service indicators which provide them with their merit payments.

Self governing hospitals

The lynch pin of the Government's new design are the self governing hospitals. In its words they will have 'a major role to play in improving services to patients'. These hospitals will remain 'firmly in the NHS'. Self governing status will be thought to be 'appropriate' for any major acute hospitals providing a reasonable comprehensive service. It will 'often be sensible for a self-governing hospital to run a range of community-based services'. There are certain considerable attractions to this idea from the point of view of the devolution of management responsibility and the greater involvement of clinicians in running their services. There are very real dangers, however, particularly to professional independence and the standards of care for children. For instance these Trust Hospitals will not have to pay any regard to the Department of Health circulars on subjects such as services for children in hospital. Paediatricians will have to think very carefully and seek further advice before they hand their contracts to untried and transient local managers.

Supraregional services

Existing supraregional services that predominantly involve children will have direct funding from the 'centre' for their fixed costs to ensure their continued viability. Variable costs will be met by general practitioners and district health authorities under contract. These variable costs will include capital charges on the valuation of expensive land and buildings in central London. The traditional referral of patients based on medical knowledge of what is right for the individual patient through personal contact is in danger of being replaced by the district health authority's preference for a cheap alternative. Careful auditing, both financial and medical, will be required of these decisions by district health authorities that may have medicolegal consequences. Indeed it is likely that one successfully fought case in the courts about a 'medical disaster' might bankrupt a Trust Hospital.

Medical audit

Medical audit is a central pillar of the Government's programme. It is defined as 'the systematic critical analysis of the quality of the medical care, including procedures used for diagnosis and treatment, use of resources and the resulting outcome and quality of life for the patient'. The Government wishes to see a comprehensive system of medical audit in place within three years and 'does not under-estimate the degree of challenge'. Its approach is firmly based on the principle that the quality of medical care can only be reviewed by a doctor's peers. The existing audit, especially that promulgated by the Royal Colleges, will be built upon. The Standing Medical Advisory Committee chaired by Sir Eric Stroud has been charged with producing a report on audit within the next few months. Little more than a basic framework is likely to be suggested in the limited time. The development of indicators of clinical outcome will take time and require a major investment in information systems. Rigid protocols based on existing inadequate data are likely to lower medical standards and stifle advances in medical care rather than improve it. On the other hand better information about the use of resources can be used by the profession to put pressure on local managers and bring medical issues into sharp focus both locally and nationally. A related issue not addressed in the Government's White Paper is a problem of medical 'negligence'. Increasingly decisions about medical outcome are being made in the court of law rather than in the conference room and recent judgments are likely to put pressure on for more defensive medicine and therefore an increasing use of expensive diagnostic tests. The department's own recommendations about the discharge of patients from hospital, for instance, are likely to have the adverse effect of increasing patients' length of stay in hospital.

Training and research

The cost of training and research will be removed from the primary decisions of the 'internal markets'. The cost of medical teaching will be 'ring-fenced' and the distribution of resources will reflect locations—not just teaching hospitals—where the medical teaching is carried out. Cross charging in respect of clinical teaching by NHS staff and the provision of patient care by clinical academics may occur. The Government recognises the technical difficulties of cost allocation between service and teaching functions should 'not be underestimated'. Hospitals are enjoined not to cut back on postgraduate training in order to achieve cost reductions if long term effects would mean poorer standards of service.

All medical advances are research based though they may be triggered by chance clinical and laboratory observations. Some new treatments involve expensive high technology but the majority, especially new drugs, have been highly cost effective. It is essential for the future development of the NHS that both pure and applied medical research are maintained and improved.

The Government will be reporting separately on the question of research in the NHS once the recommendations of the report of the House of Lords Select Committee on medical research have been considered.

· · ·

The success or failure of the Government's initiative will depend crucially on the quality of the information supporting clinicians and their staff and the involvement and commitment of the clinicians themselves to the new culture. Such a commitment by consultants, general practitioners, and other NHS staff can only be earned by the demonstration that the new system really will work for the benefit of patients.

W J Appleyard
Kent and Canterbury Hospital,
Canterbury, Kent CT1 3NG

Think about it

You make a clinical diagnosis. Do you ever consider the thought processes by which you arrived at it? Medical students and practitioners are often concerned with examples of diagnostic logic, but seldom consider them in the context of a general philosophy. Is diagnostic logic out on a limb, or is it based on the same principles as logic in general?

In *Logic in Medicine* doctors and philosophers combine to provide a coherent system of diagnostic logic with a broader view of the science and art of reasoning.

The abstract theory of theories has highly practical applications, and the authors explore the uses of computer technology and artificial intelligence systems as well as "fuzzy logic," "relevant logic," and the logic of economics and ethics. A book for all who wish to clear their minds of cant.

Price: Inland £5.95; Abroad £7.50; USA $11.50
BMA members: Inland £5.45; Abroad £7.00; USA $10.50
(including postage, by air abroad)
Payment must be enclosed with order

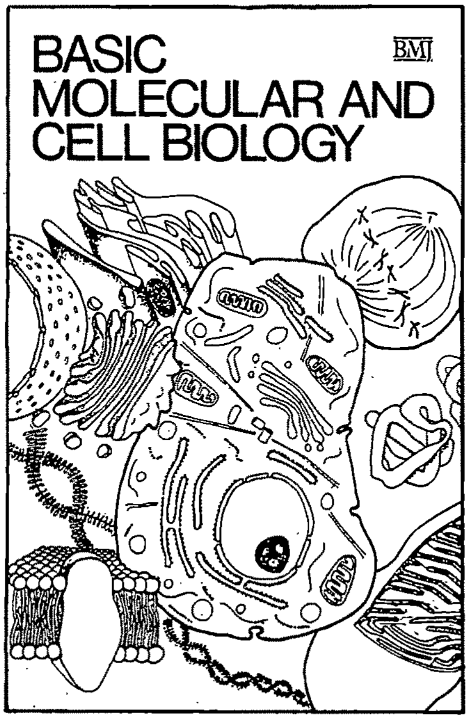
ORDER YOUR COPY NOW FROM
British Medical Journal, PO Box 295
London WC1H 9TE
or any leading medical bookseller

LOGIC IN MEDICINE

EDITED BY CALBERT PHILLIPS

BMJ

One revolution leads to another . . .



The extraordinary technical developments in molecular biology over the past few years, and the equally rapid advances in understanding of cell biology, will almost certainly result in far reaching changes in medical research and practice. In this collection of articles experts in molecular and cell biology provide the background information to give clinicians an insight into the way in which the medical sciences may be moving over the next few years and into the exciting possibilities opening up for the treatment of genetic disorders, cancer, and the common illnesses of Western society such as degenerative vascular disease and diabetes.

Price: Inland £5.95; Abroad £7.50; USA $12.00
BMA members: Inland £5.45; Abroad £7.00; USA $11.00
including postage, by air abroad
Payment must be enclosed with order.

Order from BRITISH MEDICAL JOURNAL, PO Box 295, London WC1H 9TE
or any leading medical bookseller

Two new titles from the BMJ's series of books of general interest by medical writers

The MEMOIR Club

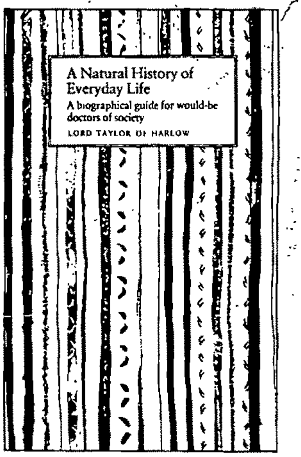
Portraits from Memory by Sir James Howie

One of the *BMJ's* most popular series, Sir James Howie's *Portraits from Memory* is now published as a complete collection. For this Memoir Club edition the author has provided three new portraits, an introductory self portrait, and an appendix in which he comments on the points raised in the widespread correspondence that resulted from the portraits' publication.

Sir James Howie's distinguished career has included appointments as professor of bacteriology in the University of Glasgow, director of the Public Health Laboratory Service, president of the Royal College of Pathologists, and president of the British Medical Association. This book is not about himself, however, but about the memorable personalities he has known in microbiology and in military, hospital, and academic medicine. Essential reading for all students of human nature.

Price: Inland £14.95; Abroad £17.50; USA $29.00. BMA members: Inland £13.95; Abroad £16.50; USA $27.00.

A Natural History of Everyday Life: A biographical guide for would-be doctors of society by Lord Taylor of Harlow



A Natural History of Everyday Life

A biographical guide for would-be doctors of society

LORD TAYLOR OF HARLOW

As doctor, politician, and administrator the late Lord Taylor was a key figure in the formative years of some varied institutions: the National Health Service; Harlow New Town (playing an important part in its development and in its industrial health service); and the Memorial University of Newfoundland, of which he was the first president and vice-chancellor. He also laid the foundations of Medicare in Canada by his skilful negotiations to resolve the doctors' strike in Saskatchewan. In his lively and provocative memoirs Lord Taylor relates his "personal voyage" from childhood, through student days at St. Thomas's to his later career in public life, providing on the way innumerable pungent observations together with his views on the origins of some of society's ills—and their cures.

Price: Inland £19.95; Abroad £24.00; USA $40.00

BMA members: Inland £18.95; Abroad £23.00; USA $38.00.

ORDER FORM

BRITISH MEDICAL JOURNAL, PO Box 295, London WC1H 9TE
or any leading medical bookseller.

Please send me the following books:

The MEMOIR Club

- ☐ **Portraits from Memory**
- ☐ **A Natural History of Everday Life**

Prices include postage, by air abroad

NAME...
Please print name and address clearly
ADDRESS...
....
....

☐ I enclose...
BMA Membership No. ....
Please make cheques payable to **British Medical Journal**
debit my credit card (*please tick box*)
☐ Access ☐ American Express ☐ Mastercard ☐
Card No. ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Card expiry date...
Signature...
☐ Please send me a book catalogue.